This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: 0 031 104
A1

(12) # EUROPEAN PATENT APPLICATION

(21) Application number: 80107869.2

(22) Date of filing: 12.12.80

(51) Int. Cl.³: C 07 D 277/06
C 07 D 207/16, A 61 K 31/425
A 61 K 31/40

(30) Priority: 13.12.79 JP 161977/79

(43) Date of publication of application:
01.07.81 Bulletin 81/26

(84) Designated Contracting States:
AT BE CH DE FR GB IT LI LU NL SE

(71) Applicant: SANTEN PHARMACEUTICAL CO., LTD.
9-19, 3-Chome, Shimoshinjo
Higashiyodogawaku Osaka(JP)

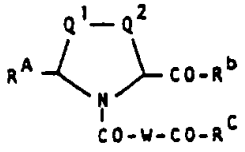
(72) Inventor: Oya, Masayuki
27-18, 3-chome Yamatedai
Ibaraki-shi Osaka(JP)

(72) Inventor: Iso, Tadashi
197-7, Joroku,
Sakai-shi Osaka(JP)

(74) Representative: Zumstein, Fritz, Dr. Dr. F. Zumstein sen. Dr. E. Assmann et al,
Dr. R. Koenigsberger Dr. F. Zumstein jun. Dipl.-Ing. F. Klingseisen Bräuhausstrasse 4
D-8000 München 2(DE)

(54) **Thiazolidine and pyrrolidine compounds, processes for their preparation and pharmaceutical compositions containing them.**

(57) Thiazolidine and pyrrolidine compounds which have the general formula



and salts thereof for preventing or relieving diabetic complications and for reducing blood pressure, the processes for their preparation, and the compositions comprising them and pharmaceutically acceptable excipient(s).

EP 0 031 104 A1

lower alkenyl, hydroxy, lower alkoxy, halogeno-lower alkoxy, acyloxy, halogen, nitro, cyano, amino, lower alkylamino, dialkylamino, acylamino, mercapto. acylmercapto, lower alkylthio, carbo: lower alkoxycarbonyl, aralkyloxycarbonyl, aryloxycarbonyl, sulfamoyl, lower alkylaminosulfonyl and lower alkylsulfinyl;

R^b is selected from the group consisting of

(a)(i) aralkyl, heteroaralkyl, aralkenyl and heteroaralkenyl, and

(ii) aralkyl, heteroaralkyl, aralkenyl and heteroaralkenyl substituted by at least one substituent selected from the group consisting of lower alkyl, lower alkenyl, halogeno-lower alkyl, hydroxy, lower alkoxy, halogeno-lower alkoxy, acyloxy, halogen, nitro, cyano, amino, lower alkylamino, dialkylamino, acylamino, mercapto, acylmercapto, lower alkylthio, carboxy, lower alkoxycarbonyl, aralkyloxycarbonyl, aryloxycarbonyl, sulfamoyl, lower alkylaminosulfonyl and lower alkylsulfinyl, and

(iii) carboxy, lower alkoxycarbonyl, aralkyloxycarbonyl, aryloxycarbonyl and heteroaryloxycarbonyl;

(b)(i) phenyl and naphthyl, and

(ii) phenyl and naphthyl substituted by at least one substituent selected from the group consisting of lower alkyl, lower alkenyl, halogeno-lower alkyl, hydroxy, lower alkoxy, halogeno-lower alkoxy, aralkyloxy, aryloxy, acyloxy, halogen, nitro, cyano, amino, lower alkylamino, dialkylamino, acylamino, mercapto, acylmercapto, lower alkylthio, carboxy, lower alkoxycarbonyl, aralkyloxycarbonyl, aryloxycarbonyl, sulfamoyl, lower alkylaminosulfonyl and lower alkylsulfinyl;

(c)(i) furyl, thienyl and pyridyl, and

(ii) furyl, thienyl and pyridyl substituted by at least one substituent selected from the group consisting of lower alkyl, lower alkenyl, halogeno-lower alkyl, hydroxy, lower alkoxy, halogeno-lower alkoxy, aralkyloxy, aryloxy, acyloxy, halogen, nitro, cyano, amino, lower alkylamino, dialkylamino, acylamino, mercapto, acylmercapto, lower alkylthio, carboxy, lower alkoxycarbonyl, aralkyloxycarbonyl, aryloxycarbonyl, sulfamoyl, lower alkylaminosulfonyl and lower alkylsulfinyl;

-O-, -CO-, -S-, -SO-, $-SO_2-$, $-C(=N-R^{20})-$, -NHCONH-, $-N\langle\rangle N-$ or $-N(R^{21})-$;

l, m, n, p, q, r, s and t each is 0, 1, 2 or 3;
R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20} and R^{21} each is R^d;

R^A is R^b when W is $-CH(R^{22})-NH-C(R^{23})(R^{24})-$ or $-CH(R^{25})-(CH)_{0-2}-CH(R^{26})-$, wherein

R^{22}, R^{23}, R^{24}, R^{25} and R^{26} each is R^d;

R^a is selected from the group consisting of
(i) hydrogen, lower alkyl and lower alkenyl, and
(ii) lower alkyl and lower alkenyl substituted by at least one substituent selected from the group consisting of lower alkyl, lower alkenyl, hydroxy, lower alkoxy, halogeno-lower alkoxy, acyloxy, halogen, nitro, cyano, amino, lower alkylamino, dialkylamino, acylamino, mercapto, acylmercapto, lower alkylthio, carboxy, lower alkoxycarbonyl, aralkyloxy-carbonyl, aryloxycarbonyl, sulfamoyl, lower alkylamino-sulfonyl and lower alkylsulfinyl;

R^b is selected from the group consisting of
(a)(i) aralkyl, heteroaralkyl, aralkenyl and heteroaralkenyl, and
(ii) aralkyl, heteroalkyl, aralkenyl and heteroaralkenyl substituted by at least one substituent selected from the group consisting of lower alkyl, lower alkenyl, halogeno-lower alkyl, hydroxy, lower alkoxy, halogeno-lower alkoxy, acyloxy, halogen, nitro, cyano, amino, lower alkylamino, dialkylamino, acylamino, mercapto acylmercapto, lower alkylthio, carboxy, lower alkoxycarbonyl, aralkyloxy-carbonyl, aryloxycarbonyl, sulfamoyl, lower alkylamino-sulfonyl and lower alkylsulfinyl, and
(iii) carboxy, lower alkoxycarbonyl, aralkyloxycarbonyl,

selected from the group consisting of lower alkyl, lower alkoxy, lower alkanoyl, acyloxy, hydroxy, carboxy, amino, halogen, nitro, cyano, acylamino, mercapto, acylmercapto, halogeno-lower alkyl, halogeno-lower alkoxy, lower alkylenedioxy, lower alkoxycarbonyl, sulfo, sulfamoyl, lower alkylaminosulfonyl and lower alkylsulfinyl

(c)(i) furyl, thienyl and pyridyl, and

(ii) furyl, thienyl and pyridyl substituted by at least one substituent selected from the group consisting of lower alkyl, lower alkoxy, lower alkanoyl, acyloxy, hydroxy, carboxy, amino, halogen, nitro, cyano, acylamino, mercapto, acylmercapto, halogeno-lower alkyl, halogeno-lower alkoxy, lower alkylenedioxy, lower alkoxycarbonyl, sulfo, sulfamoyl, lower alkylaminosulfonyl and lower alkylsulfinyl;

and salts thereof.

2. A compound of claim 1 wherein $-Q^1-Q^2-$ is $-CH_2CH_2-$, $-SCH_2-$ or $-CH_2S-$.

3. A compound of claim 1 wherein R^a is hydrogen, methyl, ethyl, 1-methylethyl, propyl, 2-methylpropyl, butyl, 2,6-dimethyl-5-heptenyl, cyclohexyl, S-acetyl-2-mercaptoethyl or 2-mercaptoethyl.

4. A compound of claim 1 wherein R^b is benzyl, 2-phenylethyl, 4-methylbenzyl, 4-methoxybenzyl, 2-hydroxybenzyl, 4-hydroxybenzyl, 3-fluorobenzyl, 3-nitrobenzyl, 3-cyanobenzyl, 2-(4-methoxyphenyl)ethyl, 2-(2-hydroxyphenyl)ethyl, 2-(4-hydroxyphenyl)ethyl, 2-(3-fluorophenyl)ethyl, 2-[3-(trifluoromethyl)phenyl]ethyl, 2-(3-nitrophenyl)ethyl, 2-(3-cyanophenyl)-ethyl, 2-pyridylmethyl, 4-pyridylmethyl, 2-furylmethyl, 2-(2-pyridyl)ethyl, 2-(4-pyridyl)ethyl, 2-(2-furyl)ethyl, phenyl, 4-methylphenyl, 2-chlorophenyl, 4-chlorophenyl, 2,4-dichlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-nitrophenyl, 3-nitrophenyl, 4-nitrophenyl, 2-chloro-5-nitrophenyl, 4-dimethyl-

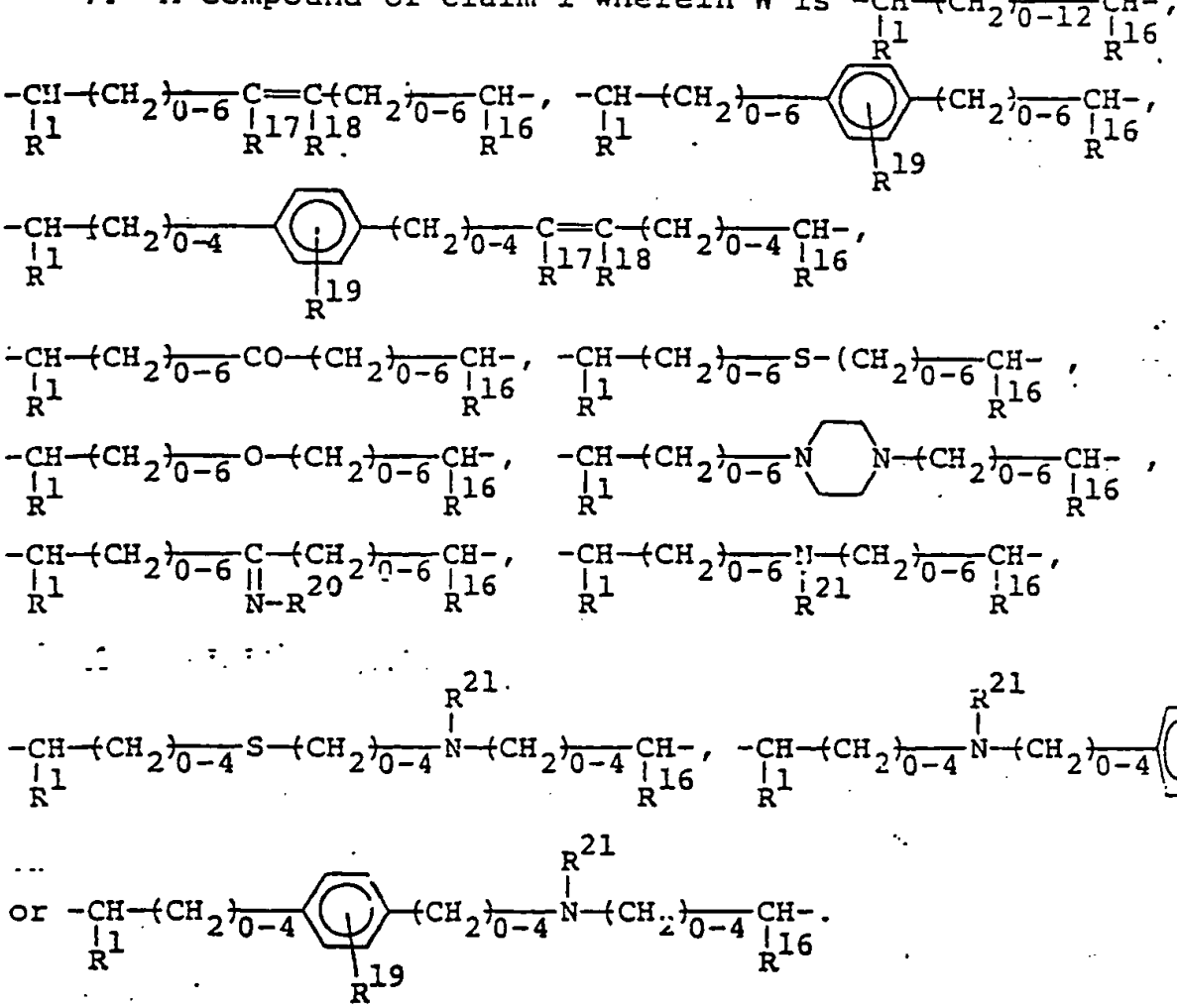
R^d is selected from the group consisting of
(a)(i) hydrogen, lower alkyl, lower alkenyl, aralkyl, hetero-aralkyl, alkanoyl, arylalkanoyl, heteroarylalkanoyl, hydroxy, carboxy, amino, mercapto and sulfo, and
(ii) lower alkyl, lower alkenyl, aralkyl, heteroaralkyl, alkanoyl, arylalkanoyl, heteroarylalkanoyl, hydroxy, carboxy, amino, mercapto and sulfo substituted by at least one substituent selected from the group consisting of lower alkyl, lower alkenyl, lower alkoxy, lower alkanoyl, aryl, heteroaryl, acyloxy, aroyl, hydroxy, carboxy, amino, guanidino, mercapto, acylamino, acylmercapto, lower alkoxycarbonyl, sulfo, halogen, nitro, cyano, sulfamoyl, lower alkylaminosulfonyl, lower alkylthio and lower alkylsulfinyl;

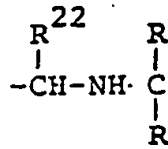
(b)(i) phenyl and naphthyl, and
(ii) phenyl and naphthyl substituted by at least one substituent selected from the group consisting of lower alkyl, lower alkoxy, lower alkanoyl, acyloxy, hydroxy, carboxy, amino, halogen, nitro, cyano, acylamino, mercapto, acylmercapto, halogeno-lower alkyl, halogeno-lower alkoxy, lower alkylenedioxy, lower alkoxycarbonyl, sulfo, sulfamoyl, lower alkylaminosulfonyl and lower alkylsulfinyl;

(c)(i) furyl, thienyl and pyridyl, and
(ii) furyl, thienyl and pyridyl substituted by at least one substituent selected from the group consisting of lower alkyl, lower alkoxy, lower alkanoyl, acyloxy, hydroxy, carboxy, amino, halogen, nitro, cyano, acylamino, mercapto, acylmercapto, halogeno-lower alkyl, halogeno-lower alkoxy, lower alkylene-dioxy, lower alkoxycarbonyl, sulfo, sulfamoyl, lower alkyl-aminosulfonyl and lower alkylsulfinyl;

and salts thereof which are useful as agents for therapy or prophylaxis of the diabetic complication because they inhibit strongly aldose reductase, and as antihypertensive agents because they inhibit angiotensin I-converting enzyme.

dihydroxyphenyl, 5-chloro-2-hydroxyphenyl, 2-methoxyphenyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, 3,4,5-trimethoxyphenyl, 2-hydroxy-3-methoxyphenyl, 2-hydroxy-5-sulfamoylphenyl, 3-(methylsulfinyl)phenyl, 3-(difluoromethoxy)phenyl, 2-furyl, 2-(5-methyl)furyl, 2-thienyl, 3-pyridyl or 4-pyridyl.

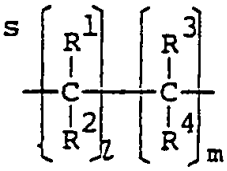
7. A compound of claim 1 wherein W is 

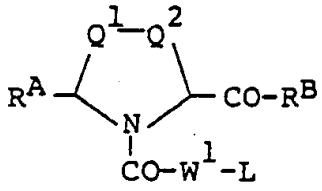
8. A compound of claim 1, wherein R^A is R^b when W is  .

9. A compound of claim 4 which is (4R)-3-[8-(ethoxycarbonyl)octanoyl]-2-(3-nitrophenyl)-4-thiazolidinecarboxylic acid.

(ii) A compound of the formula [I] is yielded by the reaction of a compound of the formula [II] with the reactive derivative of carboxylic acid of [IV] (e.g., above-mentioned)

$$HOOC\text{-}W^1\text{-}L \qquad [IV],$$

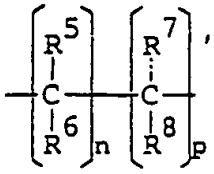
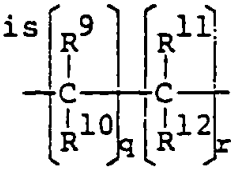
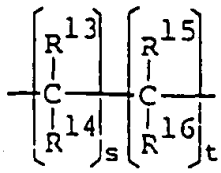
wherein W^1 is  , and may be protected such as (i) above, L is a leaving group (e.g., halogen, alkylsulfonyl, arylsulfonyl, etc.), by the same methods as described in (i) above to produce a compound of the formula [V]



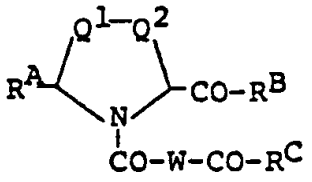
[V]

and then reation of a compound of the formula [V] with a compound of the formula [VI]

$$(H)X\text{-}W^2\text{-}Y\text{-}W^3\text{-}Z\text{-}W^4\text{-}CO\text{-}R^C \qquad [VI],$$

wherein W^2 is  , W^3 is  , W^4 is  , and W^2, W^3, W^4, X, Y, Z and R^C may be

16. A process for preparing a compound of the formula [I]



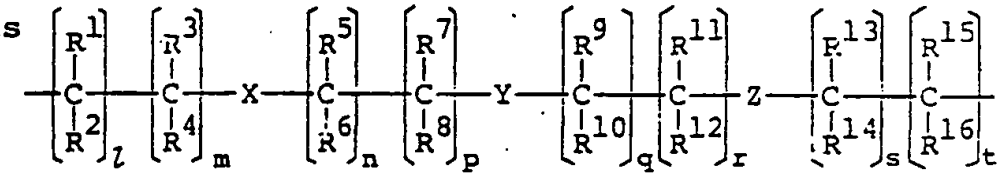
[I]

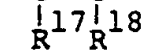
wherein

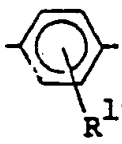
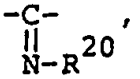
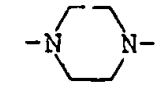
Q^1 and Q^2 each is methylene or sulfur, but Q^1 and Q^2 are not sulfur at the same time;

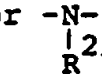
R^A is R^a or R^b;

R^B and R^C each is R^c;

W is  , wh

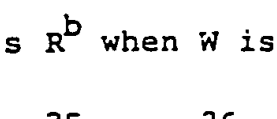
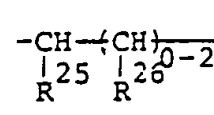
X, Y and Z each is single bond, $-CH_2-$,  , $-C\equiv C-$,

 , -O-, -CO-, -S-, -SO-, $-SO_2-$,  , -NHCONH-, 

or  ;

l, m, n, p, q, r, s and t each is 0, 1, 2 or 3;

R^1, R^2, R^3, ..., R^{20} and R^{21} each is R^d;

R^A is R^b when W is  or  , wherein R^{22}, R^{23}, R^{24}, R^{25} and R^{26} each is R^d.

(v) A compound of the formula [I] is yielded by the reaction of a compound of the formula [II] with the reactive derivative of carboxylic acid [XI] (e.g., acyl halide, acid anhydride, mixed anhydride, active ester, lactone, thiolactone, etc.)

$$HOOC-W^1-X(H) \qquad [XI],$$

and then with a compound of the formula [XII]

$$L-W^2-Y-W^3-Z-W^4-CO-R^C \qquad [XII]$$

by the same method as (ii) above.

(vi) A compound of the formula [I] is yielded by the reaction of a compound of the formula [II] with the reactive derivative of carboxylic acid of the formula [XIII] (e.g., mentioned in (v) above)

$$HOOC-W^1-X-W^2-Y(H) \qquad [XIII],$$

and then with a compound of the formula [XIV]

$$L-W^3-Z-W^4-CO-R^C \qquad [XIV]$$

by the same method as (ii) above.

(vii) A compound of the formula [I] is yielded by the reaction of a compound of the formula [II] with the

lower alkenyl, halogeno-lower alkyl, hydroxy, lower alkoxy, halogeno-lower alkoxy aralkyloxy, aryloxy, acyloxy, halogen, nitr cyano, amino, lower alkylamino, dialkylamino, acylamino, mercapto acylmercapto, lower alkylthio, carboxy, lower alkoxycarbonyl, aralkyloxycarbonyl, aryloxycarbonyl, sulfamoyl, lower alkyl-aminosulfonyl and lower alkylsulfinyl;

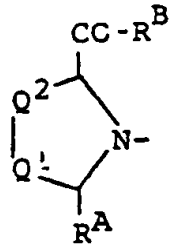
R^C is selected from the group consisting of

(a)(i) hydroxy, lower alkoxy and amino, and

(ii) lower alkoxy and amino substituted by at least one substitue selected from the group consisting of lower alkyl, aralkyl, heteroaralkyl, aralkenyl, heteroaralkenyl, hydroxy, lower alkoxy, aralkyloxy, heteroaralkyloxy, aryloxy, heteroaryloxy, acyloxy, aryl, heteroaryl, substituted aralkyl and substituted aryl wherein the substituent is lower alkyl, lower alkoxy, halogen or amino;

(b)(i) aryloxy and heteroaryloxy, and

(ii) aryloxy and heteroaryloxy substituted by at least one substituent selected from the group consisting of lower alkyl, hydroxy, lower alkoxy, halogen and amino, and

(c) 

;

R^d is selected from the group consisting of

(a)(i) hydrogen, lower alkyl, lower alkenyl, aralkyl, hetero-aralkyl, alkanoyl, arylalkanoyl, heteroarylalkanoyl, hydroxy, carboxy, amino, mercapto and sulfo, and

(ii) lower alkyl, lower alkenyl, aralkyl, heteroaralkyl, alkanoyl arylalkanoyl, heteroarylalkanoyl, hydroxy, carboxy, amino, mercapto and sulfo substituted by at least one substituent selected from the group consisting of lower alkyl, lower alkenyl, lower alkoxy, lower alkanoyl, aryl, heteroaryl, acyloxy, aroyl, hydroxy, carboxy, amino, quanidino, mercapto,

have presented that cataract is caused by the accumulation of sugar alcohols [Exptl. Eye. Res., 6, 1 (1967)]. A report of Kinoshita et al. has demonstrated that aldose reductase which reduced aldose to the corresponding sugar alcohols was involved in the initiation of these diabetic complications and that effective inhibitors of aldose reductase were useful [Jpn. J. Ophthalmol., 20, 339 (1976)]. On the basis of the above information, aldose reductase inhibition of the compounds [I] of this invention was tested. The results of the examinations demonstrated that these compounds have potent inhibitory activities on aldose reductase, and therefore they are useful as drugs for therapy or prophylaxis of the diabetic complications.

On the other hand, it has been known that a kind of the derivatives of thiazolidine- or pyrrolidinecarboxylic acid have potent inhibitory activity to angiotensin I-converting enzyme, but thiazolidine and pyrrolidine compounds of this invention are novel compounds, and have more potent inhibitory activities to angiotensin I-converting enzyme. Furthermore, the compounds of this invention are prepared by convenient methods, and are superior to the stability.

Thus, the compounds of this invention are useful as therapeutic or prophylactic agents and antihypertensive agents.

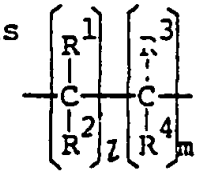
The compound of formula [I] can form the conventional

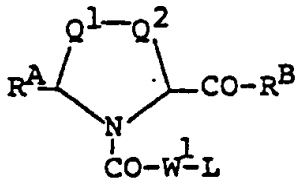
$$HOOC\text{-}W\text{-}CO\text{-}R^C \qquad [III]$$

wherein R^C and W may include suitable protection of any reacti groups, followed by removal of protective groups, if necessary to yield a compound of the formula [I];

(ii) reacting a compound of the formula [II] with the reactive derivative of carboxylic acid of the formula [IV]

$$HOOC\text{-}W^1\text{-}L \qquad [IV]$$

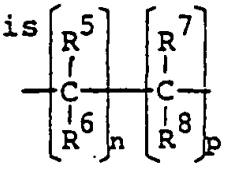
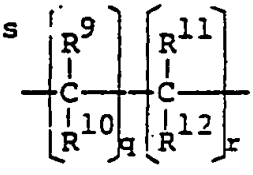
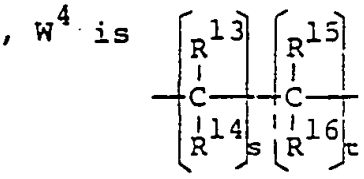
wherein W^1 is  , and may include suitable protection of any reactive groups, and L is a leaving group to yield a comp of the formula [V]



[V],

and then reacting a compound of the formula [V] with a compound of the formula [VI]

$$(H)X\text{-}W^2\text{-}Y\text{-}W^3\text{-}Z\text{-}W^4\text{-}CO\text{-}R^C \qquad [VI]$$

wherein W^2 is  , W^3 is  , W^4 is 

and W^2, W^3, W^4, X, Y, Z and R^C may include suitable protection

EXAMPLE 1

(4R)-3-(7-Carboxyheptanoyl)-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid (compound 20)

(4R)-2-(2-Hydroxyphenyl)-4-thiazolidinecarboxylic acid (6.8g,) in N sodium hydroxide (30ml) and octanedioyl dichloride (6.3g,) were added dropwise to 1M potassium carbonate (60ml) with stirring under ice-cooling. After the addition, the reaction mixture was stirred for 1 hour at the same temperature and for additional 1 hour at room temperature. The solution was acidified with dilute hydrochloric acid, and extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and evaporated in vacuo. The residual oil*2 was purified by silica gel column chromatography to give 7.0g (61%) of the titled compound: mp 155-157°C (dec.) (ethyl acetate); $[\alpha]_D^{27}$ +134.1° (c=0.5, methanol). IR (nujol, cm^{-1}): 3220 (OH), 1710 (COOH), 1620 (CON), 1600 (aromatic), 1415, 1235, 1172, 950, 760. NMR (DMSO-d_6, δ): 0.53-1.73 (8H, m, $-CH_2\underline{(CH_2)_4}CH_2-$) 1.77-2.57 (4H, m, $-\underline{CH_2}(CH_2)_4\underline{CH_2}-$), 3.03 (1H, AB_q(A part), d, J=11.5, 8.5Hz, $C_5^{*1}-H_A$), 3.37 (1H, AB_q(B part), d, J=11.5, 6.5Hz, C_5-H_B), 4.60 (1H, dd, J=8.5, 6.5Hz, C_4-H), 6.28 (1H, s, C_2-H), 6.45-8.07 (4H, m, arom. H), 9.77 (1H, s, -COOH). TLC: Rf value*3 0.52.

*1 The numbers represent the positions on thiazolidine or

$$L\text{-}W^2\text{-}Y\text{-}W^3\text{-}Z\text{-}W^4\text{-}CO\text{-}R^C \qquad [XII]$$

by the same method as (ii) above to yield a compound of the formula [I];

(vi) reacting a compound of the formula [II] with the reactive derivative of carboxylic acid of the formula [XIII]

$$HOOC\text{-}W^1\text{-}X\text{-}W^2\text{-}Y(H) \qquad [XIII],$$

and then with a compound of the formula [XIV]

$$L\text{-}W^3\text{-}Z\text{-}W^4\text{-}CO\text{-}R^C \qquad [XIV]$$

by the same method as (ii) above to yield a compound of the formula [I], or

(vii) reacting a compound of the formula [II] with the reactive derivative of carboxylic acid of the formula [XV]

$$HOOC\text{-}W^1\text{-}X\text{-}W^2\text{-}Y\text{-}W^3\text{-}Z(H) \qquad [XV],$$

and then with a compound of the formula [XVI]

$$L\text{-}W^4\text{-}CO\text{-}R^C \qquad [XVI]$$

by the same method as (ii) above to yield a compound of the formula [I];

furthermore converting R^B, R^C, X, Y and Z to other functional groups by the general methods, if desired, to obtain a desired compound of the formula [I].

17. A composition comprising a compound of the formula [I]

(4R)-3-(6-carboxyhexanoyl)-2-(4-chlorophenyl)-4-thiazolidinecarboxylic acid

(4R)-3-(7-carboxyheptanoyl)-2-(4-methoxyphenyl)-4-thiazolidinecarboxylic acid

(4R)-3-(13-carboxytridecanoyl)-2-(2-nitrophenyl)-4-thiazolidinecarboxylic acid

(4R)-3-(7-carboxyheptanoyl)-2-(3-nitrophenyl)-4-thiazolidinecarboxylic acid

(4R)-3-[3-(2-carboxyethylthio)propanoyl]-2-(3-nitrophenyl)-4-thiazolidinecarboxylic acid

(4R)-3-[[[2-(carboxymethyloxy)ethyl]oxy]acetyl]-2-(3-nitrophenyl)-4-thiazolidinecarboxylic acid

(4R)-3-(6-carboxyhexanoyl)-2-(4-nitrophenyl)-4-thiazolidinecarboxylic acid

(4R)-3-(9-carboxynonanoyl)-2-(4-nitrophenyl)-4-thiazolidinecarboxylic acid

(4R)-3-(11-carboxyundecanoyl)-2-(4-nitrophenyl)-4-thiazolidinecarboxylic acid

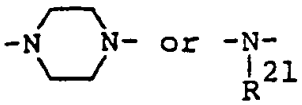
(4R)-3-[4-(3-carboxypropyloxy)butanoyl]-2-(4-nitrophenyl)-4-thiazolidinecarboxylic acid

(4R)-3-[3-(2-carboxyethylsulfonyl)propanoyl]-2-(4-nitrophenyl)-4-thiazolidinecarboxylic acid

(4R)-3-(9-carboxynonanoyl)-2-(5-chloro-2-hydroxyphenyl)-4-thiazolidinecarboxylic acid

(4R)-3-(11-carboxyundecanoyl)-2-(3,4,5-trimethoxyphenyl)-4-thiazolidinecarboxylic acid

(4R)-3-(13-carboxytridecanoyl)-2-(2-acetoxyphenyl)-4-



; ℓ, m, n, p, q, r, s and t each is 0, 1, 2 or 3; R^1, R^2, R^3, ..., R^{20} and R^{21} each is R^d;

R^a is selected from the group consisting of (i) hydrogen, lower alkyl and lower alkenyl, and (ii) lower alkyl and lower alkenyl substituted by at least one substituent selected from the group consisting of lower alkyl, lower alkenyl, hydroxy, lower alkoxy, halogeno-lower alkoxy, acyloxy, halogen, nitro, cyano, amino, lower alkylamino, dialkylamino, acylamino, mercapto, acylmercapto, lower alkylthio, carboxy, lower alkoxycarbonyl, aralkyloxycarbonyl, aryloxycarbonyl, sulfamoyl, lower alkylaminosulfonyl and lower alkylsulfinyl;

R^b is selected from the group consisting of

(a)(i) aralkyl, heteroaralkyl, aralkenyl and heteroaralkenyl, a

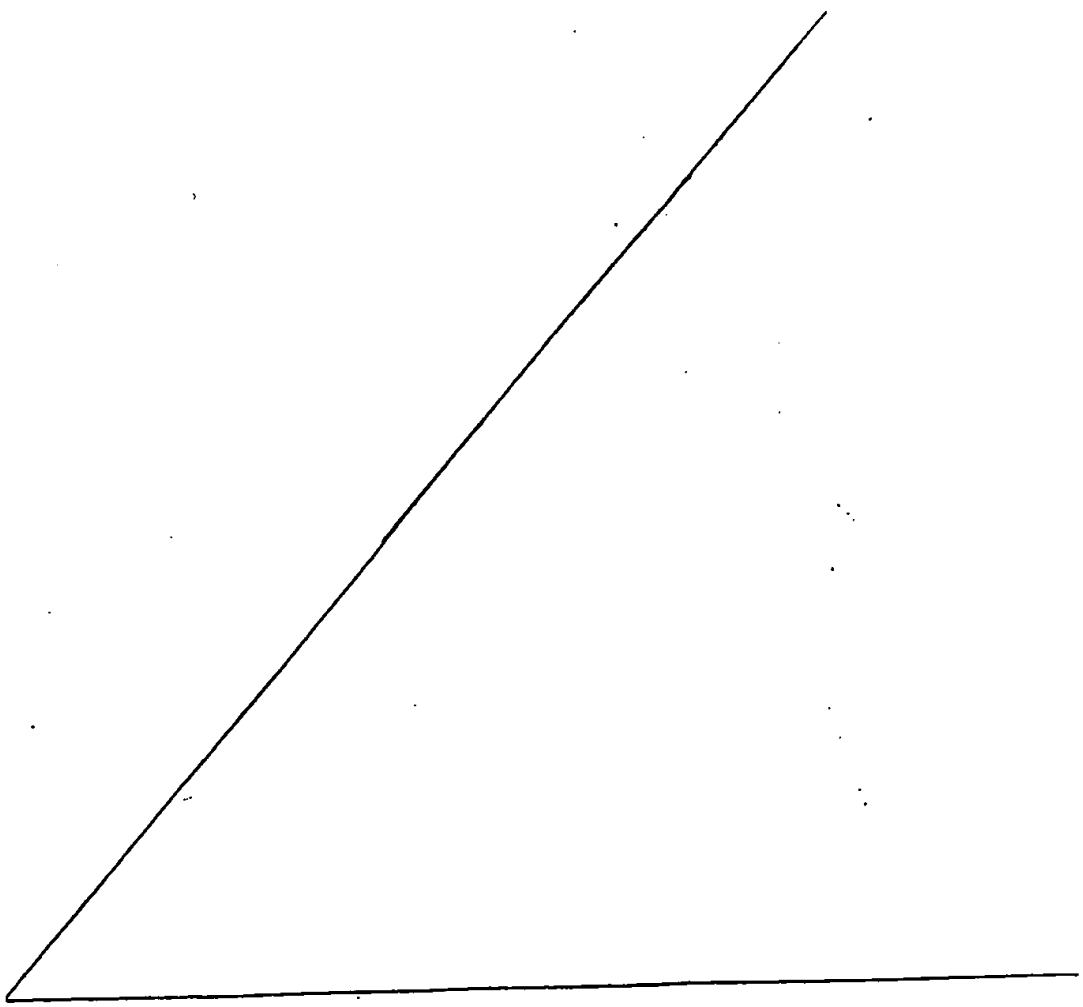
(ii) aralkyl, heteroaralkyl, aralkenyl and heteroaralkenyl substituted by at least one substituent selected from the group consisting of lower alkyl, lower alkenyl, halogeno-lower alkyl, hydroxy, lower alkoxy, halogeno-lower alkoxy, acyloxy, halogen, nitro, cyano, amino, lower alkylamino, dialkylamino, acylamino, mercapto, acylmercapto, lower alkylthio, carboxy, lower alkoxycarbonyl, aralkyloxycarbonyl, aryloxycarbonyl, sulfamoyl, lower alkylaminosulfonyl and lower alkylsulfinyl, and

(iii) carboxy, lower alkoxycarbonyl, aralkyloxycarbonyl, aryloxycarbonyl and heteroaryloxycarbonyl;

(b)(i) phenyl and naphthyl, and

(ii) phenyl and naphthyl substituted by at least one subsituent selected from the group consisting of lower alkyl, lower alkenyl, halogeno-lower alkyl, hydroxy, lower alkoxy, halogeno-lower alkoxy, aralkyloxy, aryloxy, acyloxy, halogen, nitro, cyano, amino, lower alkylamino, dialkylamino,

was added dropwise under ice-cooling. After the addition, the reaction mixture was stirred for 1 hour at the same temperature and for additional 1 hour at room temperature. The solution was acidified with dilute hydrochloric acid, extracted with ethyl acetate. The



(a)(ii) lower alkyl, lower alkenyl, aralkyl, heteroaralkyl, alkanoyl, arylalkanoyl, heteroarylalkanoyl, hydroxy, carboxy, amino, mercapto and sulfo substituted by at least one substituent selected from the group consisting of lower alkyl, lower alkenyl, lower alkoxy, lower alkanoyl, aryl, heteroaryl, acyloxy, aroyl, hydroxy, carboxy, amino, guanidino, mercapto, acylamino, acylmercapto, lower alkoxycarbonyl, sulfo, halogen, nitro, cyano, sulfamoyl, lower alkylamino-sulfonyl, lower alkylthio and lower alkylsulfinyl;

(b)(i) phenyl and naphthyl, and
(ii) phenyl and naphthyl substituted by at least one substituent selected from the group consisting of lower alkyl, lower alkoxy, lower alkanoyl, acyloxy, hydroxy, carboxy, amino, halogen, nitro, cyano, acylamino, mercapto, acyl-mercapto, halogeno-lower alkyl, halogeno-lower alkoxy, lower alkylenedioxy, lower alkoxycarbonyl, sulfo, sulfamoyl, lower alkylaminosulfonyl and lower alkylsulfinyl;

(c)(i) furyl, thienyl and pyridyl, and
(ii) furyl, thienyl and pyridyl substituted by at least one substituent selected from the group consisting of lower alkyl, lower alkoxy, lower alkanoyl, acyloxy, hydroxy, carboxy, amino, halogen, nitro, cyano, acylamino, mercapto, acylmercapto, halogeno-lower alkyl, halogeno-lower alkoxy, lower alkylenedioxy, lower alkoxycarbonyl, sulfo, sulfamoyl, lower alkylaminosulfonyl and lower alkylsulfinyl;

or salts thereof in an amount sufficient to prevent or relieve diabetes mellitus associated complications consisting of cataracts, neuropathy, nephropathy and retinopathy, and pharmaceutically acceptable excipient(s).

18. A composition comprising a compound of the formula [I]

filtered to give the precipitates. The precipitates were dissolved in hot water (100ml), and acidified with concentrated hydrochloric acid. The separated crystals were collected by filtration to give 3.5g (59%) of the titled compound: mp 105-112°C; $[\alpha]_D^{25}$ +115.0° (c=1.0, methanol). IR (nujol, cm^{-1}): 2270 (CN), 1735 (COOH), 1640 (CON), 1610 (aromatic), 1195, 790 (aromatic). NMR (DMSO-d_6) δ: 0.69-1.66 (6H, m, $-CH_2\underline{(CH_2)_3}CH_2-$), 1.70-2.50(4H, m, $-\underline{CH_2}(CH_2)_3\underline{CH_2}-$), 2.85-3.66 (4H, m, C_5-H), 4.69 (1H, dd, J=8.2, 6.0Hz, C_4-H), 5.13(1H, m, C_4-H), 6.16 (1H, s, C_2-H), 6.43 (1H, s, C_2-H), 7.3-8.3 (8H, m, arom. H). TLC: Rf value* 0.33.

* Silica gel, ethyl acetate-chloroform-acetic acid (10:5:3).

The compounds shown in Table II were prepared by the same procedure as described above.

The following compounds are also prepared by the same procedure as EXAMPLE 2 or 3.

(4R,4'R)-3,3'-(propanedioyl)bis(4-thiazolidinecarboxylic acid)

(4R,4'R)-3,3'-(butanedioyl)bis(2-phenyl)-4-thiazolidinecarboxylic acid)

(4R,4'R)-3,3'-(3,3'-sulfinyldipropanoyl)bis[2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid]

(4R,4'R)-3,3'-[(ethylenedioxy)diacetyl]bis[2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid]

(4R,4'R)-3,3'-[(ethylenedithio)diacetyl]bis[2-(2-hydroxy-

R^{23}, R^{24}, R^{25} and R^{26} each is R^d;

R^a is selected from the group consisting of
(i) hydrogen, lower alkyl and lower alkenyl, and
(ii) lower alkyl and lower alkenyl substituted by at least one substituent selected from the group consisting of lower alkyl, lower alkenyl, hydroxy, lower alkoxy, halogeno-lower alkoxy, acyloxy, halogen, nitro, cyano, amino, lower alkylamino, dialkylamino, acylamino, mercapto, acylmercapto, lower alkylthio, carboxy, lower alkoxycarbonyl, aralkyloxycarbonyl, aryloxycarbonyl, sulfamoyl, lower alkylaminosulfonyl and lower alkylsulfinyl;

R^b is selected from the group consisting of
(a)(i) aralkyl, heteroaralkyl, aralkenyl and heteroaralkenyl,
(ii) aralkyl, heteroaralkyl, aralkenyl and heteroaralkenyl substituted by at least one substituent selected from the group consisting of lower alkyl, lower alkenyl, halogeno-lower alkyl, hydroxy, lower alkoxy, halogeno-lower alkoxy, acyloxy, halogen, nitro, cyano, amino, lower alkylamino, dialkylamino, acylamino, mercapto, acylmercapto, lower alkylthio, carboxy, lower alkoxycarbonyl, aralkyloxycarbonyl, aryloxycarbonyl, sulfamoyl, lower alkylaminosulfonyl and lower alkylsulfinyl, and
(iii) carboxy, lower alkoxycarbonyl, aralkyloxycarbonyl, aryloxycarbonyl and heteroaryloxycarbonyl;

(b)(i) phenyl and naphthyl, and
(ii) phenyl and naphthyl substituted by at least one substituent selected from the group consisting of lower alkyl, lower alkenyl, halogeno-lower alkyl, hydroxy, lower alkoxy, halogeno-lower alkoxy, aralkyloxy, aryloxy, acyloxy, halogen, nitro, cyano, amino, lower alkylamino, dialkylamino, acylamino, mercapto, acylmercapto, lower alkylthio, carboxy, lower alkoxycarbonyl, aralkyloxycarbonyl, aryloxycarbonyl, sulfamoyl, lower alkylsulfonyl and lower alkylsulfinyl;

(4R,4'R)-3,3'-(tetradecanedioyl)bis[2-(2-acetoxyphenyl)-4-thiazolidinecarboxylic acid]

(4R,4'R)-3,3'-(heptanedioyl)bis[2-(2-furyl)-4-thiazolidinecarboxylic acid]

(4R,4'R)-3,3'-(octanedioyl)bis[2-(2-thienyl)-4-thiazolidinecarboxylic acid]

(4R,4'R)-3,3'-(nonanedioyl)bis[2-(3-pyridyl)-4-thiazolidinecarboxylic acid]

(4R,4'R)-3,3'-(decanedioyl)bis[2-(1-naphtyl)-4-thiazolidinecarboxylic acid]

(4R,4'R)-3,3'-(hexanedioyl)bis[2-(2-hydroxy-5-sulfamoylphenyl)-4-thiazolidinecarboxylic acid]

(4R,4'R)-3,3'-(octanedioyl)bis[2-(3-difluoromethoxyphenyl)-4-thiazolidinecarboxylic acid]

(4R,4'R)-3,3'-(nonanedioyl)bis[2-(4-carboxyphenyl)-4-thiazolidinecarboxylic acid]

(4R,4'R)-3,3'-(decanedioyl)bis[2-(3-methylsulfinylphenyl)-4-thiazolidinecarboxylic acid].

EXAMPLE 4

(4R,4'R)-3,3'-(Heptanedioyl)bis[2-(3-nitrophenyl)-4-thiazolidinecarboxylic acid] (compound 35)

To a stirred solution of (4R)-2-(3-nitrophenyl)-4-thiazolidinecarboxylic acid (5.1g) in 1M sodium carbonate (40ml), heptanedioyl dichloride (2.1g) was added dropwise under ice-cooling. The

one substituent selected from the group consisting of lower alkyl, lower alkenyl, lower alkoxy, lower alkanoyl, aryl, heteroaryl, acyloxy, aroyl, hydroxy, carboxy, amino, quanidino, mercapto, acylamino, acylmercapto, lower alkoxycarbonyl, sulfo, halogen, nitro, cyano, sulfamoyl, lower alkylaminosulfonyl, lower alkylthio and lower alkylsulfinyl;

(b)(i) phenyl and naphthyl, and
(ii) phenyl and naphthyl substituted by at least one substituent selected from the group consisting of lower alkyl, lower alkoxy, lower alkanoyl, acyloxy, hydroxy, cabroxy, amino, halogen, nitro, cyano, acylamino, mercapto, acylmercapto, halogeno-lower alkyl, halogeno-lower alkoxy, lower alkylenedioxy, lower alkoxycarbonyl, sulfo, sulfamoyl, lower alkylaminosulfonyl and lower alkylsulfinyl;

(c)(i) furyl, thienyl and pyridyl, and
(ii) furyl, thienyl and pyridyl substituted by at least one substituent selected from the group consisting of lower alkyl, lower alkoxy, lower alkanoyl, acyloxy, hydroxy, carboxy, amino, halogen, nitro, cyano, acylamino, mercapto, acylmercapto, halogeno-lower alkyl, halogeno-lower alkoxy, lower alkylenedioxy, lower alkoxycarbonyl, sulfo, sulfamoyl, lower alkylaminosulfonyl and lower alkylsulfinyl;

or salts thereof in an amount sufficient to reduce blood pressure and pharmaceutically acceptable excipient(s).

19. A compound according to claim 1 to 16 for use in a method for therapy or prophylaxis.

20. Use of a compound according to claim 1 to 16 in a process for producing pharmaceutical compositions.

(OH), 1720 (COOH), 1618 (CON), 1602 (aromatic), 1245, 1173, 940, 763. NMR (DMSO-d_6,δ): 2.0-2.7 (4H, m, -$\underline{CH_2CH_2}$-), 3.03 (1H, AB_q(A part), d, J=11.0, 10.0Hz, C_5-H_A), 3.36 (1H, AB_q (B part), d, J=11.0, 7.0Hz, C_5-H_B), 4.61 and 5.07 (1H, dd, J=10.0, 7.0Hz and m, C_4-H), 6.36 (1H, s, C_2-H), 6.5-8.0 (4H, arom. H). TLC: Rf value* 0.35.

* Silica gel, ethyl acetate-chloroform-acetic acid (10:5:3).

The compounds shown in Table I and III were prepared by the same procedure as described above. The following compounds are also prepared by the same procedure as EXAMPLE 5.

(4R)-3-(4-carboxy-4-oxobutanoyl)-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid

(4R)-3-(6-carboxy-3,5-dioxohexanoyl)-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid

(4R)-3-[4-carboxy-3-(methoxyimino)butanoyl]-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid.

EXAMPLE 6

(4R)-3-[3-(Methoxycarbonyl)-2-methylpropanoyl]-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid (compound 4)

To a stirred solution of (4R)-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid (11.3g) in 1M sodium carbonate (80mL), dl-3-methoxycarbonyl-2-methylpropanoyl chloride (8.2g) was added dropwise under ice-cooling.

(ethyl acetate); $[\alpha]_D^{25}$ +174.1° (c=1.0, methanol). IR (nujol, cm^{-1}): 3330 (OH), 1730 and 1710 (COOH), 1629 (CON), 1280, 1234, 856, 771.

The compounds shown in Table I and II were prepared by the same procedure as described above. The following compounds are also prepared by the same procedure as EXAMPLE 6 and 7.

(4R)-3-[4-(carboxymethyl)benzoyl]-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid

(4R)-3-[(4-carboxyphenyl)acetyl]-2-phenyl-4-thiazolidine-carboxylic acid

(4R)-3-(4-carboxy-3-butenoyl)-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid

(4R)-3-(4-carboxy-2-butenoyl)-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid

(4R)-3-(4-carboxy-3-butynoyl)-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid

EXAMPLE 8

(4R)-3-[3-(N-Hydroxycarbamoyl)propanoyl]-2-(2-hydroxy-phenyl)-4-thiazolidinecarboxylic acid ethyl ester (compound 10a)

To a stirred solution of (4R)-3-(3-carboxypropanoyl)-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid ethyl ester (compound 8a) (1.06g) and N-methylmorpholine (0.33ml)

in 20ml of anhydrous tetrahydrofuran, isobutyl chloroformate (0.39ml) was added dropwise at -15°C, and stirred for additional 2 hours at this temperature. To this solution, the methanol solution of hydroxylamine (0.3g) was added dropwise at -50°C. The reaction mixture was stirred for 1 hour at room temperature, acidified with N hydrochloric acid, and extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residual oil was purified by silica gel column chromatography to give 0.7g (63%) of the titled compound. IR (KBr, cm^{-1}) 3220, 1727, 1625, 1595, 1200, 1092, 753. NMR (acetone-d_6, δ): 1.24 (3H, t, J=7.5Hz, $CO_2CH_2\underline{CH_3}$), 2.17-3.07 (4H, m, $CO-(\underline{CH_2})_2-CO$), 3.30 (1H, AB_q(A part), d, J=10.0, 2.0Hz, C_5-H_A), 3.47 (1H, AB_q(B part), d, J=10.0, 7.0Hz, C_5-H_B), 4.14 (2H, q, J=7.5Hz, $CO_2\underline{CH_2}$), 5.18 (1H, dd, J=2.0, 7.0Hz, C_4-H), 6.40 (1H, S, C_2-H), 6.88-7.27 (4H, m, arom. H), 8.60 (2H, br. s, $NH\underline{OH}$), 9.77 (1H, br. s, $O\underline{H}$)

The compounds shown in Table I were prepared by the same procedure as described above.

EXAMPLE 9

(4R,4'R)-3,3'-(Nonanedioyl bis[2-(3-nitrophenyl)-4-thiazolidinecarboxylic acid methyl ester] (compound 46)

To a stirred solution of (4R,4'R)-3,3'-(nonanedioyl)bis-[2-(3-nitrophenyl)-4-thiazolidinecarboxylic acid] (compound 47) (3.3g) in ethyl acetate (50ml), 2% ether solution of diazomethane was added dropwise until the yellow color of diazomethane was not disappeared, and stirred continuously for 30 minutes. The reaction mixture was concentrated in vacuo to give 3.3g (96%) of the titled compound: mp 61-63°C (benzene); $[\alpha]_D^{23}$ +79.4° (c=1.0, methanol). IR (KBr, cm^{-1}): 1740, 1660, 1530, 1350, 1198, 725.

EXAMPLE 10

(4R)-3-[(2-Carboxymethylthio-3-phenyl)propanoyl]-4-thiazolidinecarboxylic acid (compound 75a and 75b)

(4R)-3-[(2-Mercapto-3-phenyl)propanoyl]-4-thizolidine-carboxylic acid (1.0g), potassium carbonate (0.7g), chloroacetic acid (0.2g) and potassium iodide (0.05g) were dissolved in water (5ml), and stirred for 6 hours at room temperature. The reaction mixture was acidified with 5N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate and concentrated in vacuo. The titled compounds (75a and 75b) were separated from the oily residue by silica gel column chromatography.

	75a	75b
yield	0.4g (37%)	0.5g (47%)
$[\alpha]_D^{25}$	-52.2° (c=1.2, MeOH)	-60.4° (c=1.0, MeOH)
IR (neat, cm-1)	1720, 1620, 1422, 1217, 756	1722, 1620, 1420, 1215, 755
NMR ($CDCl_3$, δ)	2.67-3.63 (6H, m, $-S-CH_2-CO_2H$, C_5-H, $-CH_2-Ph$), 3.83-4.83 (3H, m, $-CO-CH-S-$, C_2-H), 4.98 (1H, dd, J=4.5, 6.5Hz, C_4-H), 7.22 (5H, s, $-C_6H_5$) 9.55 ($-CO_2H$)	2.70-3.50 (6H, m, $-S-CH_2-CO_2H$, C_5-H, $-CH_2-Ph$), 4.00-4.57 (3H, m, $-CO-CH-S-$, C_2-H) 5.02 (1H, dd, J=4.5, 9.5Hz, C_4-H), 7.23 (5H, s, $-C_6H_5$), 10.00 ($-CO_2H$)

The compounds shown in Table IV were prepared by the same procedure as described above.

EXAMPLE 11

(4R)-3-[(Carboxymethylamino)acetyl]-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid (compound 81)

(4R)-3-Chloroacetyl-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid (6g) was added to a stirred solution of glycine (1.5g) in N sodium hydroxide (80ml), and stirred overnight at room temperature. The solution was adjusted to pH 1.5 by 20% hydrochloric acid and washed with ethyl acetate. The aqueous layer was adjusted to pH 3.2, and

the separated crystals were collected by filtration to 3.28g (48.2%) of the titled compound: mp 181-182°C (dec.) (water); $[\alpha]_D^{24}$ +271.2° (c=0.5, MeOH). IR (KBr, cm^{-1}): 3400, 3200, 1740, 1672, 1560, 1440, 1380, 1335, 1212, 752, 648, NMR (K_2CO_3 in D_2O, δ): 3.0-4.3 (6H, m, C_5-H, $COCH_2NHCH_2CO_2H$), 6.33 and 6.43 (1H, each s, C_2-H), 6.6-7.3 (3H, m, arom. H), 7.82 (1H, br. d, J=8Hz, arom. H), 9.0-10.3 (2H, br. s, -OH, $-CO_2H$).

The compounds shown in Table V were prepared by the same procedure as described above.

EXAMPLE 12

(2S)-1-[[(2S)-2-Bis(ethoxycarbonylmethyl)amino]propanoyl]-2-pyrrolidinecarboxylic acid benzyl ester (compound 88)

Ethyl bromoacetate (0.92g) was added dropwise under ice-cooling to a stirred solution of L-alanyl-L-proline benzyl ester p-toluenesulfonate (2.24g) and triethylamine (1.53ml) in dry methylenechloride. After the addition, the reaction mixture was stirred for 2 hours at room temperature, refluxed for another 5 hours, and washed with water and saturated sodium chloride solution. The organic layer was dried over anhydrous magnesium sulfate and concentrate in vacuo. The residual oil was purified by silica gel column chromatography to give 1.02g (44.8%) of the titled

compound: $[\alpha]_D^{24}$ -67.9° (c=1.2, MeOH). IR (neat, cm^{-1}): 3460, 1742, 1642, 1428, 1180. NMR ($CDCl_3$, δ): 1.23 (6H, t, J=7Hz, $-CO_2CH_2\underline{CH_3}$), 1.25 (3H, d, J=7.2Hz, CO-$\underset{\underline{CH_3}}{CH}$-N), 1.67-2.40 (4H, m, C_3-H and C_4-H), 3.57 (4H, s, -N-$\underline{CH_2}CO_2Et$), 3.50-4.00 (2H, m, C_5-H), 4.13 (4H, q, J=7Hz, $-COCH_2\underline{CH_3}$), 4.10-4.67 (2H, m, C_2-H and -CO-$\underset{\underline{CH_3}}{\underline{CH}}$-N), 5.03, 5.20 (2H, AB_q, J=12Hz, $-\underline{CH_2}$-Ph), 7.30 (5H, s, $-C_6\underline{H_5}$).

The compounds shown in Table V were prepared by the same procedure as described above.

EXAMPLE 13

(2S)-1-[[(2S)-Bis(ethoxycarbonylmethyl)amino]propanoyl]-2-pyrrolidinecarboxylic acid (compound 86)

(2S)-1-[[(2S)-2-bis(ethoxycarbonylmethyl)amino]propanoyl]-2-pyrrolidinecarboxylic acid benzyl ester (compound 88) (0.50g) was dissolved in ethanol (10ml), and hydrogenated with 10% palladium on charcoal catalyst (50mg). The titled compound was obtained as a colorless oil. Yield 0.40g (quant. yild); $[\alpha]_D^{24}$ -52.2° (c=1.1, MeOH). IR (neat, cm^{-1}): 1742, 1640, 1442, 1190, 1130, 752. NMR ($CDCl_3$, δ): 1.23 (6H, t, J=7Hz, $-CO_2CH_2\underline{CH_3}$), 1.25 (3H, d, J=7.2Hz, COCH-N), 1.67-2.50 (4H, m, C_3-H and C_4-H),

3,53 (4H, s, N-CH_2-CO_2Et), 3.50-4.00 (2H, m, C_5-H), 4.10 (4H, q, J=7Hz, -$CO_2CH_2CH_3$), 4.10-4.33 (1H, m, -COCH(CH$_3$)-N), 4.47 (1H, dd, J=6.5, 5.0Hz, C_2-H), 9.20 (1H, br. s, -CO_2H).

The compounds shown in Table V were prepared by the same procedure as described above. The following compouds are also prepared by the same procedure as EXAMPLE 12 and 13.

(2S)-1-[[4-(1-carboxy-3-phenylpropyl)amino]benzoyl]-2-pyrrolidinecarboxylic acid.

(4R)-3-[[4-(1-carboxy-3-phenylpropyl)amino]benzoyl]-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid

EXAMPLE 14

(2S)-1-[[(2S)-2-(N-Ethoxycarbonylmethyl-N-phenylacetyl)-amino]propanoyl]-2-pyrrolidinecarboxylic acid benzyl ester (compound 90)

Phenylacetyl chloride (0.44ml) was added dropwise at room temperature to a stirred solution of (2S)-1-[[(2S)-2-(ethoxycarbonylmethyl)amino]propanoyl]-2-pyrrolidinecarboxylic acid benzyl ester (1.1g) and triethylamine (0.47ml) in dry acetone (15ml). After the addition, the reaction mixture was stirred for 1 hour at the same temperature, and the precipitate was removed by filtration. The filtrate was evaporated in vacuo, and the residual oil was dissolved in ethyl acetate, and washed with water and

saturated sodium chloride solution. The organic layer was dried over anhydrous magnesium sulfate, and evaporated in vacuo. The residual oil was purified by silica gel column chromatography to give 1.3g (89%) of the titled compound: mp 110-110.5°C (benzene-hexane); $[\alpha]_D^{24}$ -114.0° (c=1.0, MeOH). IR (KBr, cm^{-1}): 3460, 1739, 1635, 1436, 1200, 1166. NMR ($CDCl_3$, δ): 1.23 (3H, d, J=7Hz, -CO-CH(CH$_3$)-N), 1.28 (3H, t, J=7Hz, $-CO_2CH_2\underline{CH_3}$), 1.67-2.50 (4H, m, C_3-H and C_4-H), 3.60 (2H, s, $-COCH_2Ph$), 3.33-3.90 (2H, m, C_5-H), 4.16 (2H, q, J=7Hz, $-COCH_2CH_3$), 4.23 (2H, s, $-N-CH_2CO_2Et$), 4.30-4.60 (1H, m, C_2-H), 5.03, 5.23 (2H, AB_q, J=12.5Hz, $-CO_2CH_2Ph$), 5.58 (1H, q, J=7Hz, -COCH(CH$_3$)-N), 7.23 (5H, s, $-COCH_2C_6H_5$), 7.30 (5H, s, $-CO_2CH_2C_6H_5$).

The compounds shown in Table V were prepared by the same procedure as described above.

EXAMPLE 15

(2S)-1-[(2S)-2-[(1-Carboxy-3-phenylpropyl)thio]propanoyl]-2-pyrrolidinecarboxylic acid (compound 79)

(2S)-1-[(2S)-2-Mercaptopropanoyl]-2-pyrrolidine-carboxylic acid (2.0g), potassium carbonate (2.8g) and 2-bromo-4-phenylbutanoic acid (2.9g) were dissolved in water (40ml), and stirred overnight at room temperature. The

reaction mixture was acidified with 6N hydrochloric acid, and extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residual oil was purified by silica gel column chromatography to give 2.3g (62%) of the titled compound: $[\alpha]_D^{23}$ -82.2° (c=1.2, MeOH). IR (KBr, cm^{-1}): 1740, 1720, 1610, 1455, 1438, 1185, 748, 700.

The compounds shown in Table IV were prepared by the same procedure as described above.

EXAMPLE 16

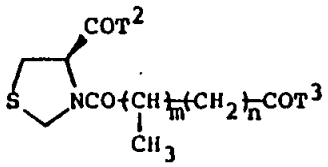
1-[[(1-Carboxy-3-phenylpropyl)amino]acetyl]-2-(2-hydroxyphenyl)-5-pyrrolidinecarboxylic acid (compound 99)

1-(Chloroacetyl)-5-(2-hydroxyphenyl)-2-pyrrolidinecarboxylic acid [mp 204-206°C(dec.), $[\alpha]_D^{24}$ +24.5° (c=1.2, MeOH)] (2.8g) was added to a stirred solution of 2-amino-4-phenylbutanoic acid (1.8g) in N sodium hydroxide (40ml). The reaction mixture was stirred overnight at room temperature. The solution was adjusted to pH 1.5 by 20% hydrochloric acid, and washed with ethyl acetate. The aqueous layer was adjusted to pH 3.0, and the separated solid was collected by filtration to give 1.0g (24%) of the titled compound. IR (nujol, cm^{-1}): 3425, 1735, 1625, 1588.

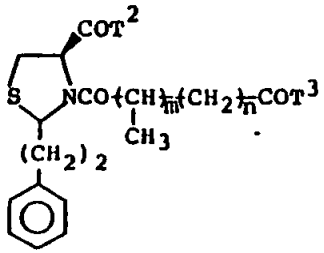
The compounds shown in Table V were prepared by the same procedure as described above.

In EXAMPLEs and TABLEs I, II, III, IV and V, "a" and "b" of compound No. represent diastereoisomers each other. TABLEs I, II, III, IV and V show various compounds and their physical constants including the compounds specified in EXAMPLEs.

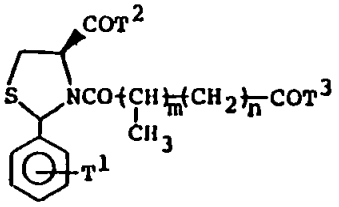
Table I



Compound No. 1



Compound No. 2a and 2b



Compound 3-32

Compd. No.†	T^1	T^2	T^3	m	n	Method of prepn. (Examp. No.)	Yield (%)	mp (°C) (Recrystn. solvent)	$[\alpha]_D$ deg. (c, solv., °C)	IR spectrum: Sampling method*1	IR spectrum: cm^{-1}	Rf value*2 (SiO_2)
1		OH	OH	0	6	1	55	oil	-84.3 (0.8, MeOH, 26)	C	1720, 1605, 1420, 1190, 1015, 880	0.39
2a		OH	OH	0	3	5	26	oil	-19.8 (1.1, MeOH, 24)	C	1733, 1710, 1650, 1600, 1410, 1240, 1040	0.60*3
2b		OH	OH	0	3	5	51	oil	-113.8 (1.1, MeOH, 24)	C	1730, 1650, 1610, 1410, 1240, 1042	0.55*3
3	2-OH	OH	OH	0	1	1	65	154.0-154.5 (dec.) (H_2O)	+201.4 (0.7, MeOH, 25)	B	3340, 1725, 1625, 1600, 1460, 1430, 1235, 1100, 915, 770	0.25
4	2-OH	OH	OMe	1	1	6	44	oil	+161.6 (1.0, MeOH, 25)	A	3380, 1723, 1624, 1235, 1200, 1174, 764	0.51
5	2-OH	OH	OH	1	1	7	75	163-164 (dec.) (EtOAc)	+174.1 (1.0, MeOH, 25)	B	3330, 1730, 1710, 1629, 1280, 1234, 856, 771	0.41

Table-continued

Compd.† No.	T^1	T^2	T^3	m	n	Method of prepn. (Examp. No.)	Yield (%)	mp (°C) (Recrystn. solvent)	$[\alpha]_D$ deg. (c, solv., °C)	IR spectrum: Sampling*1 method	IR spectrum: cm^{-1}	Rf value*2 (SiO_2)
6	2-OH	OH	OH	0	2	1 5	75	190-191 (dec.) (EtOAc-MeOH)	+181.6 (1.0, MeOH, 27)	B	3210, 1720, 1618, 1602, 1245, 1173, 940, 763	0.35
7	2-OH	OH	OMe	0	2	6	83	165-166 (dec.) (EtOAc)	+164.5 (1.0, MeOH, 25)	A	3370, 1750, 1693, 1635, 1215, 1165, 755	0.47
8a	2-OH	OEt	OH	0	2	5	45	181-182 (EtOAc)	-2.8 (0.5, MeOH, 21)	A	3310, 1727, 1703, 1637, 1595, 1235, 1190, 745	0.55
8b	2-OH	OEt	OH	0	2	5	23	116-118 (EtOAc)	-311.6 (0.5, MeOH, 21)	A	3370, 1735, 1708, 1635, 1597, 1220, 1180, 760	0.55
9a	2-OH	OH	NHOH	0	2	7		172-173 (dec.) (EtOH-H_2O)		A	3375, 3290, 1720, 1657, 1625, 1590, 1240, 1088, 748	0.22
9b	2-OH	OH	NHOH	0	2	7		amorph.		A	3220, 1717, 1655, 1625, 1595, 1225, 1092, 752	0.33
10a	2-OH	OEt	NHOH	0	2	8		amorph.		A	3220, 1727, 1625, 1595, 1200, 1092, 753	0.25*4
10b	2-OH	OEt	NHOH	0	2	8		amorph.				0.32*4
11*5	2-OH	OH	OMe	1	2	6		amorph.	+55.5 (0.8, MeOH, 24)	B	1738, 1630, 1585, 1310, 1258, 750	
11a*5	2-OH	OH	OMe	1	2	6		205-207 (dec.) (benzene)	+94.6 (0.5, MeOH, 23)	B	3110, 1730, 1625, 1610, 1192, 1121, 758	
12a	2-OH	OH	OH	1	2	7	79	168-170 (dec.) (acetone-cyclohexane)	+168.0 (0.4, MeOH, 23)	A	3370, 1718, 1625, 1598, 758	0.25*4
12b	2-OH	OH	OH	1	2	7		163-164 (dec.) (acetone-cyclohexane)	+149.2 (0.4, MeOH, 23)	A	3300, 1720, 1708, 1615, 1598, 1242, 753	0.25*4
13	2-OH	OH	OH	0	3	5	65	161-162 (dec.) (H_2O)	+153.8 (0.5, MeOH, 24)	B	3190, 1713, 1632, 1598, 1253, 1098, 943, 760	0.38
14	2-OH	OH	OEt	0	3	6	88	157-158 (dec.) (EtOAc-benzene)	+145.6 (1.0, MeOH, 25)	A	3340, 1725, 1638, 1597, 1218, 1120, 768	0.48
15	H	OH	OH	0	3	5	73	139-140 (EtOAc-MeOH)	+106.3 (1.0, MeOH, 24)	B	3170, 1753, 1709, 1631, 1423, 1177, 729	0.39

Table-continued

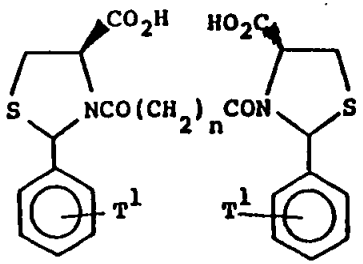
Compd. No.*	T^1	T^2	T^3	m	n	Method of prepn. (Examp. No.)	Yield (%)	mp (°C) (Recrystn. solvent)	$[\alpha]_D$ deg. (c, solv., °C)	IR spectrum: Sampling method*1	IR spectrum: cm^{-1}	Rf value*2 (SiO_2)
16	4-CN	OH	OH	0	3	5	59	190-191 (EtOAc-MeOH)	+137.7 (1.0, MeOH, 24)	B	2225, 1710, 1665, 1412, 1258	0.31
17	2-OH	OH	OH	0	4	1	62	amorph.	+115.6 (1.0, MeOH, 24)	B	3300, 1700, 1622, 1595, 760, 723	0.43
18	2-OH	OH	OH	0	5	1	60	158-159 (dec.) (EtOAc)	+128.6 (0.5, MeOH, 25)	B	3300, 1710, 1620, 1595, 1280, 1095, 895, 850, 760	0.47
19	H	OH	OH	0	6	1	33	oil	+80.5 (1.0, MeOH, 24)			0.50
20	2-OH	OH	OH	0	6	1	61	155-157 (dec.) (EtOAc)	+134.1 (0.5, MeOH, 27)	B	3220, 1710, 1620, 1600, 1415, 1235, 1172, 950, 760	0.52
21	2-OH	OH	OH	0	7	1	63	153-154 (dec.) (EtOAc)	+70.9 (0.5, MeOH, 26)	B	3220, 1705, 1620, 1600, 1415, 1235, 1173, 1090, 830, 760	0.55
22	3-NO_2	OH	OH	0	7	1	45	oil	+72.1 (0.4, MeOH, 27)	C	1710, 1615, 1525, 1405, 1350, 1095, 735	0.56
23	3-NO_2	OH	OEt	0	7	6	79	oil	+72.8 (1.0, MeOH, 23)	C	1735, 1663, 1620, 1533, 1352, 1240, 1190, 728	0.57
24	2-F	OH	OH	0	7	1	53	oil	+69.9 (0.5, MeOH, 23)	C	1730, 1660, 1625, 1587, 1228, 1043, 756	0.57
25	3-F	OH	OH	0	7	1	50	oil	+63.4 (0.5, MeOH, 23)	C	1730, 1655, 1610, 1590, 1243, 1042, 775	0.57
26	4-F	OH	OH	0	7	1		oil	+57.9 (0.8, MeOH, 23)			0.51*4
27	2-Cl 5-NO_2	OH	OH	0	7	1	45	amorph.	+108.3 (0.5, MeOH, 23)	A	1720, 1660, 1580, 1526, 1240, 1050, 745	0.57

Table-continued

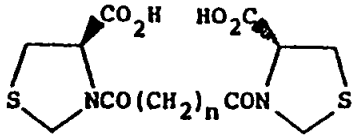
Compd. No.†	T^1	T^2	T^3	m	n	Method of prepn. (Examp. No.)	Yield (%)	mp (°C) (Recrystn. solvent)	$[\alpha]_D$ deg. (c, solv., °C)	IR spectrum: Sampling*1 method	IR spectrum: cm-1	Rf value*2 (SiO_2)
28	2-OH	OH	OH	0	8	1	58	oil	+100.3 (1.0, MeOH, 24)	C	1710, 1620, 1600, 1410, 1230, 1090, 850, 760	0.58
29	2-OH	OH	OH	0	10	1	55	123-124 (EtOAc-cyclohexane)	+120.4 (0.5, MeOH, 25)	B	3320, 1705, 1620, 1595, 1410, 1233, 1090, 943, 850, 760	0.61
30	3-CN	OH	OH	0	10	1	56	oil	+56.4 (0.3, MeOH, 23)			0.56*4
31	2-OH	OH	OH	0	12	1	59	amorph.	+101.4 (1.0, MeOH, 24)	B	3280, 1700, 1620, 1575, 760,722	0.52
32	3-CN	OH	OH	0	12	1	43	oil	+61.7 (0.6, MeOH, 23)			0.53*4

† a and b represent diastereoisomers of the compound.
*1 A; KBr disk, B; nujol mull, C; neat.
*2 EtOAc-$CHCl_3$-AcOH (10:5:3).
*3 $CHCl_3$-EtOH-AcOH (10:2:1).
*4 EtOAc-$CHCl_3$-AcOH (7:5:1).
*5 Dicyclohexylamine salt.

Table II



Compound No. 33-37, 39-62



Compound No. 38

Compd. No.	T^1	n	Method of prepn. (Examp. No.)	Yield (%)	mp (°C) (Recrystn. solvent)	$[\alpha]_D$ deg. (c, solv., °C)	IR spectrum: Sampling*1 method	IR spectrum: cm^{-1}	Rf value*2 (SiO_2)
33	2-OH	4	2	73	124-128 (MeOH)	+182.2 (1.0, DMF, 24)	B	3280, 1726, 1620, 1596, 775,	0.23
34	2-OH	5	2	67	oil	+106.1 (0.5, MeOH, 26)	C	1725, 1625, 1600, 1410, 1235, 1095, 1045, 850, 765	0.27
35	3-NO_2*5	5	4	69	111-113 (dec.) (H_2O)	+88.2 (0.5, MeOH, 25)	B	1635, 1585, 1520, 1355 1095, 730	0.28
36	3-CN	5	3	59	105-112 (H_2O)	+115.0 (1.0, MeOH, 25)	B	2270, 1735, 1640, 1610, 1195, 790	0.33
37	4-CN	5	3	52	amorph.	+148.2 (0.9, MeOH, 25)	B	2255, 1731, 1655, 1620, 785	0.32
38		6	2	77	oil	-124.5 (0.5, MeOH, 26)	C	1720, 1580, 1410, 1180, 1015, 880	0.09
39	H	6	2	79	amorph.	+97.4 (1.0, MeOH, 24)	B	1720, 1625, 1585, 732	0.42

Table-continued

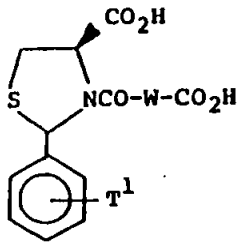
Compd. No.	T[1]	n	Method of prepn. (Examp. No.)	Yield (%)	mp (°C) (Recrystn. solvent)	$[\alpha]_D$ deg. (c, solv., °C)	IR spectrum: Sampling method[*1]	IR spectrum: cm-1	Rf value[*2] (SiO_2)
40	2-OH	6	2	86	amorph.	+123.6 (0.5, MeOH, 27)	B	1720, 1620, 1600, 1230, 1090, 855, 765	0.34
41	3-NO_2	6	2	56	amorph.	+97.5 (0.5, MeOH, 21)	B	1730, 1650, 1605, 1520, 1345, 1095, 730	0.34
42	3-CN	6	2	58	amorph.	+98.3 (0.9, MeOH, 25)	B	2250, 1730, 1640, 1615, 1200, 790	0.38
43	4-CN	6	2	41	amorph.	+130.2 (0.9, MeOH, 25)	B	2248, 1729, 1650, 1618, 790	0.36
44	2-OH	7	2	75	amorph.	+142.7 (0.5, MeOH, 26)	B	1720, 1620, 1600, 1410, 1230, 1173, 1090, 855, 763	0.40
45	2-NO_2	7	2	47	amorph.	+191.2 (0.6, MeOH, 25)	B	1735, 1655, 1515, 1345, 1190, 730	0.38
46[*6]	3-NO_2	7	9	96	61-63 (benzene)	+79.4 (1.0, MeOH, 23)	A	1740, 1660, 1530, 1350, 1198, 725	0.57
47	3-NO_2	7	2	82	amorph.	+96.2 (0.5, MeOH, 27)	B	1725, 1615, 1520, 1445, 1350, 1095, 730	0.41
48	4-NO_2	7	2	53	amroph.	+118.5 (0.5, MeOH, 25)	B	1730, 1650, 1600, 1510, 1345, 1185, 1110, 735	0.48
49	3-CN	7	3	65	amorph.	+112.1 (1.1, MeOH, 25)	B	2250, 1729, 1640, 1610, 790	0.41
50[*5]	2-F	7	4	85	140-220 (dec.) (H_2O)	+117.5 (1.0, MeOH, 24)	A	1580, 1225, 1173, 758	0.50
51[*5]	3-F	7	4	88	195-210 (dec.) (H_2O)	+103.9 (0.5, MeOH, 25)	A	1590, 1238, 1142, 767	0.50
52	4-F	7	2	76	oil	+75.8 (1.0, MeOH, 23)			0.39[*3]

Table-continued

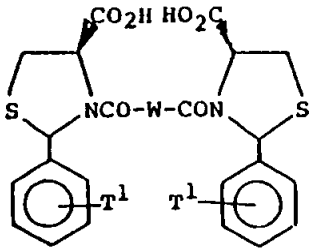
Compd. No.	T[1]	n	Method of prepn. (Examp. No.)	Yield (%)	mp (°C) (Recrystn. solvent)	$[\alpha]_D$ deg. (c, solv., °C)	IR spectrum: Sampling*1 method	IR spectrum: cm^{-1}	Rf value*2 (SiO_2)
53	2-Cl 5-NO_2	7	2	79	amorph.	+167.9 (0.5, MeOH, 23)	A	1725, 1640, 1575, 1520, 1342, 1047, 740	0.51
54	2-OH 5-SO_2NH_2	7	2	75	amorph.	+140.9 (0.6, MeOH, 23)	B	1725, 1620, 1595, 1310, 1150, 930	0.42*4
55	2-OH	8	2	68	amorph.	+122.1 (1.0, MeOH, 24)	B	3300, 1730, 1628, 1575, 767, 725	0.45
56	3-CN	8	2	47	amorph.	+104.6 (1.0, MeOH, 25)	B	2245, 1726, 1630, 1610, 790	0.37
57	3-NO_2	8	2	84	amorph.	+102.2 (0.5, MeOH, 25)	A	1735, 1620, 1523, 1190, 728	0.47
58*5	3-NO_2	8	4	74	amorph.	+93.9 (0.5, MeOH, 23)	A	1597, 1520, 1269, 1096, 723	
59	2-OH	10	2	61	99-100.5 (dec.) (EtOAc-benzene)	+124.7 (0.5, MeOH, 27)	B	3300, 1740, 1620, 1600, 1565, 1230, 1160, 1090, 895, 770	0.49
60*5	3-CN	10	4	63	190-195 (H_2O)	+109.3 (0.5, H_2O, 23)	B	3400, 2240, 1640, 1600, 1208, 778, 720	
61	2-OH	12	2	66	amorph.	+69.5 (1.0, MeOH, 24)	B	3300, 1728, 1630, 1590, 762, 725	0.45
62*5	3-CN	12	4	52	amorph.	+104.2 (0.5, MeOH, 23)	B	3400, 2225, 1605, 1320, 1207, 775, 720	0.46*3

*1 A; KBr disk, B; nujol mull, C; neat.
*2 EtOAc-$CHCl_3$-AcOH (10:5:3).
*3 EtOAc-$CHCl_3$-AcOH (7:5:1).
*4 $CHCl_3$-MeOH-AcOH (3:1:1).
*5 Disodium salt.
*6 Dimethyl ester.

Table III



Compound No. 63-68



Compound No. 69-71

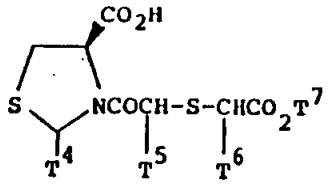
Compd. No.	T^1	W	Method of prepn. (Examp. No.)	Yield (%)	mp (°C) (Recrystn. solvent)	$[\alpha]_D$ deg. (c, solv., °C)	IR spectrum: Sampling*1 method	IR spectrum: cm-1	Rf value*2 (SiO_2)
63	2-OH	$-CH_2COCH(COCH_3)-$	5	31	amorph.	+149.2 (1.2, MeOH, 25)	B	1743, 1720, 1630, 1600, 1238	0.38*3
64	2-OH	$-CH_2-O-CH_2-$	1	35	amorph.	+138.6 (1.1, MeOH, 25)	A	3300, 1726, 1640, 1453, 1234, 1142	0.24*4
65	3-NO_2	$-(CH_2)_2-C_6H_4-(CH_2)_2-$	1	36	amorph.	+81.7 (0.9, MeOH, 24)	A	3400, 1702, 1618, 1525, 1400, 1347	0.55*3
66	2-OH	$-(CH_2)_2-O-(CH_2)_2-$	1	33	136-137 (EtOAc)	+147.6 (0.5, MeOH, 25)	B	3320, 1750, 1710, 1625, 1595, 1235, 1110, 855, 770	0.28
67	2-OH	$-(CH_2)_2-S-(CH_2)_2-$	1	40	159-160 (dec.) (EtOAc)	+136.4 (0.5, MeOH, 27)	B	3360, 1710, 1627, 1599, 1435, 1235, 1099, 852, 763	0.42
68	2-OH	$-(CH_2)_2-S-(CH_2)_2-S-(CH_2)_2-$	1	35	amorph.	+78.1 (1.0, MeOH, 24)	B	3300, 1715, 1627, 1590, 760	0.31
69	3-NO_2	$-(CH_2)_2-C_6H_4-(CH_2)_2-$	2	44	amorph.	+106.9 (1.1, MeOH, 24)	A	3425, 1730, 1640, 1525, 1400, 1350	0.38*3

Table-continued

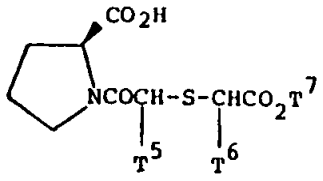
Compd. No.	T[1]	W	Method of prepn. (Examp. No.)	Yield (%)	mp (°C) (Recrystn. solvent)	$[\alpha]_D$ deg. (c, solv., °C)	IR spectrum: Sampling method*1	IR spectrum: cm-1	Rf value*2 (SiO_2)
70	2-OH	$-(CH_2)_2-O-(CH_2)_2-$	2	47	amorph.	+83.0 (0.5, MeOH, 26)	B	1720, 1625, 1600, 1230, 1090, 850, 760	0.15
71	2-OH	$-(CH_2)_2-S-(CH_2)_2-$	2	53	amorph.	+129.3 (0.5, MeOH, 27)	B	1720, 1620, 1600, 1420, 1230, 1093, 852, 763	0.30

*1 A; KBr disk, B; nujol mull.
*2 EtOAc-$CHCl_3$-AcOH (10:5:3).
*3 EtOAc-EtOH-AcOH (40:1:1).
*4 $CHCl_3$-EtOH-AcOH (10:2:1).

Table IV



Compound No. 72-76



Compound No. 77-80

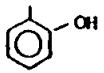
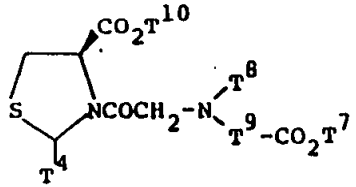
Compd. No.†	T^4	T^5	T^6	T^7	Method of prepn. (Examp. No.)	Yield (%)	mp (°C) (Recryetn. solvent)	$[\alpha]_D$ deg. (c, solv., °C)	IR spectrum: Sampling*1 method	IR spectrum: cm-1	Rf value*2 (SiO_2)
72a	H	CH_3	Ph	H	10	30	151-153 (EtOAc)	+8.6 (1.0, MeOH, 23)	A	3030, 1737, 1720, 1615, 1413, 1215, 1150, 717	0.26*3
72b	H	CH_3	Ph	H	10	49	oil	-161.5 (1.0, MeOH, 23)	C	1735, 1623, 1413, 1243, 1170, 1043, 699	0.22*3
73		H	CH_2CH_2Ph	H	10	81	amorph.	+122.1 (1.2, MeOH, 25)	A	1720-1710, 1625, 1600, 1400, 1235, 752, 698	0.74
74	H	CH_3	CH_2CH_2Ph	H	10	52	amorph.	-97.9 (1.1, MeOH, 25)	A	1720, 1620, 1415, 750, 700	0.65
75a	H	CH_2Ph	H	H	10	37	oil	-52.2 (1.2, MeOH, 25)	C	1720, 1620, 1422, 1217, 756	0.13*4
75b	H	CH_2Ph	H	H	10	46	oil	-60.4 (1.0, MeOH, 25)	C	1722, 1620, 1420, 1215, 755	0.13*4
76	H	CH_2CH_2Ph	H	H	10	84	oil	-61.2 (1.3, MeOH, 24)	C	1735, 1630, 1615, 1420, 1242, 1172, 1043, 702	0.66

Table-continued

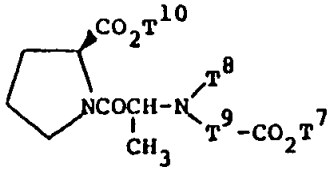
Compd. No.†	T^4	T^5	T^6	T^7	Method of prepn. (Examp. No.)	Yield (%)	mp (C°) (Recrystn. solvent)	$[\alpha]_D$ deg. (c, solv., °C)	IR spectrum: Sampling*1 method	IR spectrum: cm-1	Rf value*2 (SiO_2)
77		H	COPh	Et	15	36	oil	-46.2 (0.8, MeOH, 30)	C	1733, 1678, 1632, 1610, 1447, 1258, 1187, 1025, 1001, 751	0.32*3
78		H	CH_2CH_2Ph	H	15	46	oil	-48.4 (1.1, MeOH, 26)	C	1730, 1610, 1450, 1240, 1190, 750, 703	0.72*5
79		CH_3	CH_2CH_2Ph	H	15	62	amorph.	-82.2 (1.2, MeOH, 23)	A	1740, 1720, 1610, 1455, 1438, 1185, 748, 700	0.38
80		H	$COCH_3$	Et	15	45	oil	-49.6 (0.9, MeOH, 30),	C	1736, 1597, 1398, 1378, 1333, 1250, 1191, 1047, 860, 752	0.29*3

† a and b represent diastereoisomers of the compound.
*1 A; KBr disk, C; neat.
*2 EtOAc-$CHCl_3$-AcOH (10:5:3).
*3 Benzene-EtOAc-EtOH-AcOH (14:14:2:1).
*4 Benzene-EtOAc-AcOH (25:25:1).
*5 $CHCl_3$-EtOH-AcOH (10:2:1)

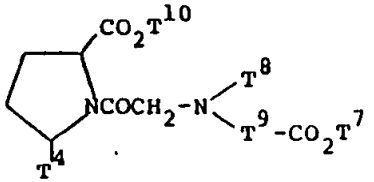
Table V



Compound No. 81-85



Compound No. 86-98, 100-102



Compound No. 99

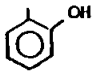
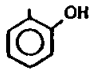
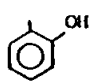
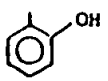
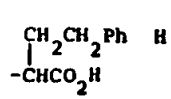
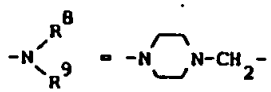
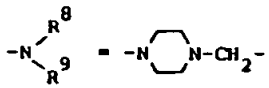
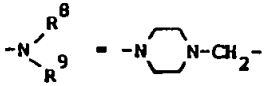
Compd. No.†	T^4	T^7	T^8	T^9	T^{10}	Method of prepn. (Examp. No.)	Yield (%)	mp (°C) (Recrystn. solvent)	$[\alpha]_D$ deg. (c, solv., °C)	IR spectrum Sampling method*1	IR spectrum cm^{-1}	Rf value (SiO_2)
81		H	H	$-CH_2-$	H	11	48.2	181-182 (dec.) (H_2O)	+271.2 (0.5, N NaOH, 24)	A	3400, 3200, 1740, 1672, 1560, 1440, 1380, 1335, 1210, 752	0.25*2
82		H	H	$-CH_2-$	H	11	32.8	150-155 (H_2O)	+94.7 (0.5, N NaOH, 23)	B	3420, 3210, 1650, 1240, 839, 790	0.45*3
83		H	H		H	11	44.8	150-153 (dec.) (EtOH-ether)	+86.5 (0.4, MeOH, 26)	A	3370-2900, 1655, 1602, 1175	0.74*4
84		H	H		H	11	50.3	172-173 (dec.) (EtOAc)	+78.9 (0.8, MeOH, 25)	A	3350, 1720, 1670, 1644, 1236, 744	0.69*4
85		H	H		H	11	27.2	174-175 (dec.) (H_2O)		A	3400, 1720, 1660, 1610, 1492, 1452, 1240, 752, 700	
86	H	Et	CH_2CO_2Et	$-CH_2-$	H	13	quant.	oil	-52.2 (1.1, MeOH, 24)	C	1742, 1640, 1442, 1190, 1130, 752	0.21*5

Table-continued

Compd.† No.	T^4	T^7	T^8	T^9	T^{10}	Method of prepn. (Examp. No.)	Yield (%)	mp (°C) (Recrystn. solvent)	$[\alpha]_D$ deg. (c, solv., °C)	IR spectrum: Sampling method*1	IR spectrum: cm^{-1}	Rf value (SiO_2)
87	H	H	CH_2CO_2H	$-CH_2-$	H	7	26	amorph.	-32.8 (1.0, MeOH, 24)	B	3400, 1720, 1640, 1460, 1380	0.10*2
88	H	Et	CH_2CO_2Et	$-CH_2-$	CH_2Ph	12	45.2	oil	-67.9 (1.2, MeOH, 24)	C	3460, 1742, 1642, 1428, 1180	0.70*5
89a	H	H	H		H	16	33	216-218 (dec.) (H_2O)	-141.1 (0.3, MeOH, 23)	B	2600, 1743, 1550, 1250, 1230, 800	0.20*6
89b	H	H	H		H	16	45	218-226 (dec.) (H_2O)	+1.5 (0.5, MeOH, 23)	B	3310, 1610, 1575, 1160, 742	0.20*6
90	H	Et	$COCH_2Ph$	$-CH_2-$	CH_2Ph	14	89	110-110.5 (benzene-*n*-hexane)	-114.0 (1.0, MeOH, 24)	A	3460, 1739, 1635, 1436, 1200, 1166	0.45*7
91	H	Et	$COCH_2Ph$	$-CH_2-$	H	13	quant.	oil	-99.7 (1.1, MeOH, 23)	D	1743, 1640, 1445, 1187	0.35*5
92	H	H	$COCH_2Ph$	$-CH_2-$	H	7	83	205-206 (EtOAc-MeOH)	-123.5 (1.0, MeOH, 24)	A	3430, 1727, 1635, 1598, 1426, 1184	0.38*8
93	H	Et	$CO(CH_2)_2Ph$	$-CH_2-$	CH_2Ph	14	93	oil	-93.2 (1.0, MeOH, 24)	C	1746, 1655, 1647, 1447, 1188	0.51*7
94	H	Et	$CO(CH_2)_2Ph$	$-CH_2-$	H	13	quant.	oil	-94.7 (1.2, MeOH, 23)	D	1746, 1642, 1449, 1190,	0.38*5
95	H	H	$CO(CH_2)_2Ph$	$-CH_2-$	H	7	96	amorph.	-104.3 (1.0, MeOH, 24)	A	3440, 1735, 1610, 1450, 1185	0.45*8
96	H	Et	CH_2Ph	$-CH_2-$	CH_2Ph	12	46	oil	-66.0 (1.2, MeOH, 25)	D	1740, 1639, 1450, 1425, 1185	0.57*7
97	H	H	CH_2Ph	$-CH_2-$	H	7	87	amorph.	-59.0 (1.1, MeOH, 25)	A	3420, 1720, 1638, 1448, 1385	0.17*2
98	H	H	$COCH_3$	CH_2CH_2Ph | $-CHCO_2H$	H	14	62	195-196 (dec.) (EtOAc)		B	1758, 1720, 1615, 1600, 1380, 750, 700	

Table-continued

Compd.† No.	T^4	T^7	T^8	T^9	T^{10}	Method of prepn. (Examp. No.)	Yield (%)	mp (°C) (Recrystn. solvent)	$[\alpha]_D$ deg. (c, solv., °C)	IR spectrum: Sampling*1 method	IR spectrum: cm^{-1}	Rf value (SiO_2)
99*11		H		H	H	16	24	amorph.		B	3425, 1735, 1625, 1588	0.66*2
100	H	Et			CH_2Ph	14	37	oil	-46.9 (0.5, MeOH, 23)	C	1740, 1642, 1453, 1425, 1170, 740	0.20*9
101	H	Et			H	13	90	oil	-35.9 (0.5, MeOH, 23)			0.25*2
102	H	H			H	7	90	228-230 (dec.) (MeOH)	-33.9 (0.4, MeOH, 23)	B	3450, 1720, 1610, 1305, 1228, 1200, 680	0.34*10

† a and b represent diastereoisomers of the compound.

*1 A; KBr disk, B; nujol mull, C; Neat, D; liquid cell ($CHCl_3$).

*2 *n*-BuOH-AcOH-H_2O (4:2:1).

*3 *n*-BuOH-AcOH-H_2O (4:1:2).

*4 EtOAc-$CHCl_3$-AcOH (10:5:3).

*5 EtOAc-EtOH-AcOH (40:1:1).

*6 EtOAc-$CHCl_3$-AcOH (7:5:1).

*7 Benzene-EtOAc-AcOH (25:25:1).

*8 $CHCl_3$-EtOH-AcOH (10:2:1).

*9 EtOAc

*10 *n*-Propanol-28% aq. NH_3 (7:3).

*11 Starting material: 1-(chloroacetyl)-5-(2-hydroxyphenyl)-2-pyrrolidinecarboxylic acid; mp 204-206°C (dec.), $[\alpha]_D^{24}$ +24.5° (c=1.2, MeOH), IR (nujol, cm^{-1}) 3370, 1698, 1645, 1610, 1595, 1238, 758.

PHARMACOLOGICAL TEST 1

It has been known that aldose reductase participates in diabetic cataract which is one of the diabetic complications and that appearance is retarded or depressed by inhibition of the aldose reductase [Acta Societatis Ophthalmologicae Japonicae, 80, 1362 (1976)]. The following method is used for the present test.

(Method)

Aldose reductase is purified from rat lenses according to the method of Hoyman et al. [J. Biol. Chem., 240, 877 (1965)]. Action of the compounds (I) of this invention is evaluated by measurement of optical density according to the J.H. Kinoshita's method [Invest. Ophthal., 13, 713 (1974)]. The reaction mixture for the measurement of the aldose reductase activity is 3.0ml [0.067M phosphate buffer solution (pH 6.2), 0.46M lithium sulfate, 5 x 10^{-5}M NADPH, 4 x 10^{-4}M DL-glyceraldehyde, 10U aldose reductase, 10^{-4} to 10^{-10}M the compounds (I)] as total volume, and the absorbance thereof is measured at 340nm.

(Result)

Table VI shows that the compounds (I) of this invention have a strong aldose reductase inhibition effect.

Table VI. Inhibitory Activity of the Thiazolidine Compounds against Aldose Reductase

Compd. No.	IC_{50} (M) *1
22	8.2×10^{-10}
23	1.1×10^{-8}
47	1.6×10^{-10}
56	1.7×10^{-9}
57	5.4×10^{-9}
Control *2	1.0×10^{-7}

*1 Molar concentration of a compound producing 50% inhibition of aldose reductase.

*2 Quercitrin: referred to Acta Societatis Ophthalmologicae Japonicae, 80, 1369-1370 (1976).

PHARMACOLOGICAL TEST 2

As the method of measurement of angiotensin I-converting enzyme activity, bioassay for the contractile response of isolated smooth muscle or the pressor response of normal animals and biochemical assay for the enzyme isolated from lung or other organs of animals are known. The former is found more advantageous than the latter for the examination of the convertion of angiotensin I to angiotensin II in vivo.

In the present study, therefore, we adopted the bioassay for contractile response of isolated guinea pig ileum to angiotensin I.

(Method)

Isolated guinea pig ileum was suspended in the organ bath containing 20ml of Tyrode's solution of 30°C gassed with 95% O_2 + 5% CO_2. The contraction induced by the addition of angiotensin I (0.1µg/ml) at intervals of 10 minutes was recorded on a recticorder (Nihon Koden) for 90 seconds using FD pick up (ST-1T-H, Nihon Koden)

The test compounds were added to the bath 5 minutes before the addition of angiotensin I.

The inhibitory activity of angiotensin I-converting enzyme was calculated by the following formula.

$$\frac{A - B}{A} \times 100$$

A: contractile intensity of angiotensin I before addition of the compound

B: contractile intensity of angiotensin I after addition of the compound

From the fact that kininase II, which destroys bradykinin having contractive action on isolated guinea pig ileum, is thought to be identical with angiotensin I-converting enzyme augmentation of the contractile response to bradykinin by test compounds was examined

by using bradykinin (0.005μg/ml) in place of angiotensin I according to the above mentioned method.

(Result)

Concentration of a number of the compounds of this invention, which produced 50% inhibition of angiotensin I activity or augmentation of bradykinin activity inducing the contraction of guinea pig ileum, fell in the range of 10^{-7} ~ 10^{-9}M.

PHARMACOLOGICAL TEST 3

The activity of angiotensin I-converting enzyme was measured by spectrophotometry according to the method of D.W. Cushman and H.S. Cheung [Biochem. Pharmacol., 20, 1637 (1971)]. That is, the absorbance of hippuric acid was measured, which is liberated by incubating hippuryl-L-histidyl-L-leucine (HHL) as substrate in the presence of angiotensin I-converting enzyme extracted from rabbit lung.

(Method)

The reaction mixture is as follows:

100mM phosphate buffer (pH 8.3)

300mM sodium chloride

5mM HHL

10^{-3} ~ 10^{-9}M enzyme inhibitor

5mU enzyme

0.25ml of the above mixture was incubated at 37°C for 30 minutes and the reaction was stopped by adding 0.25ml of 1 N hydrochloric acid. To this solution, 1.5ml of ethyl acetate was added in order to extract hippuric acid. 1.0ml of ethyl acetate layer was collected and evaporated to dryness, and the residue obtained was dissolved in 1.0ml of water. The absorbance of this solution was measured at 228nm.

The inhibitory activity of angiotensin I-converting enzyme was calculated by the following formula:

$$\text{Percent inhibition} = \frac{A - B}{A} \times 100$$

A: absorbance of reaction solution before addition of the compound

B: absorbance of reaction solution after addition of the compound

Concentration of compound producing 50% inhibition of angiotensin I-converting enzyme (IC_{50})

The solution containing compounds at the concentration of 1×10^{-3}M to 1×10^{-9}M was incubated and percent inhibition at each concentration was calculated according to the above formula, and then IC_{50}, concentration of the compound producing 50% inhibition of the enzyme activity, was determined.

(Result)

IC_{50} of a number of the compounds of this invention,

fell in the range of $10^{-7} \sim 10^{-10}$M.

TOXICITY TEST

The acute toxicity of compounds 47 and 56 is 1000 ~ 1500mg/kg.

(Experimental animals)

The male ddy-std. strain mice (4 weeks of age, weighing 19-21g) were placed in a breeding room of constant temperature and humidity (23±1°C, 55±5%) and fed freely pellet diet (CE-2, Clea Japan, Inc.) and water ad. libitum for a week. The mice showing the normal growth were selected for the experiment.

(Method of administration)

Test compounds are dissolved in distilled water and administered (i.v.) in a dose of 0.5ml/20g body weight.

It is found in the above pharmacological and toxicity test that the compounds (I) of this invention are useful as drugs for therapy or prophylaxis of the diabetic complications and as antihypertensive agents.

In case the compounds are used for preventing or relieving diabetic complications, the dosage forms are tablet, capsule, granule, powder, suppository, injection, ophthalmic solution, ophthalmic ointment, etc. These preparations can also contain general excipients.

On the other hand, in case the compounds are used for reducing blood pressure, they can be given with the combination of diuretics such as probenecid, carinamide, hydroflumethiazide, furosemide, and bumetanide same as other antihypertensive agents. The compounds can be administered either orally or parenterally. The dosage forms are tablet, capsule, granule, powder, suppository, injection, etc. In the treatment of hypertension, these preparations can contain not only general excipients but also other antihypertensive agents such as reserpine, α-methyldopa, guanethidine, clonidine, hydralazine, etc., or β-adrenergic blocking agents such as propranolol, alprenolol, pindolol, bufetolol, bupranolol, bunitrolol, practolol, oxprenolol, indenolol, timolol, bunolol, etc.

The dose is adjusted depending on symptom, dosage form, etc. But, usual daily dosage is 1 to 5000mg, preferably 10 to 1000mg, in one or a few divided doses.

EXAMPLES OF FORMULATION

(1) Oral drug

(a) tablet

compound 13	50mg
lactose	120mg
crystalline cellulose	60mg
calcium carboxymethylcellulose	7mg
magnesium stearate	3mg
Total	240mg

compound 22	100mg
lactose	95mg
crystalline cellulose	45mg
calcium carboxymethylcellulose	7mg
magnesium stearate	3mg
Total	240mg

compound 23	150mg
lactose	60mg
crystalline cellulose	30mg
calcium carboxymethylcellulose	7mg
magnesium stearate	3mg
Total	250mg

compound 56	150mg
lactose	60mg
crystalline cellulose	30mg
calcium carboxymethylcellulose	7mg
magnesium stearate	3mg
Total	250mg

compound 74	150mg
lactose	60mg
crystalline cellulose	30mg
calcium carboxymethylcellulose	7mg

magnesium stearate	3mg
Total	250mg

compound 88	150mg
lactose	60mg
crystalline cellulose	30mg
calcium carboxymethylcellulose	7mg
magnesium stearate	3mg
Total	250mg

The tablets may be treated with common film-coating and further with sugar-coating.

(b) granule

compound 13	30mg
polyvinylpyrrolidone	25mg
lactose	385mg
hydroxypropylcellulose	50mg
talc	10mg
Total	500mg

compound 22	30mg
polyvinylpyrrolidone	25mg
lactose	385mg
hydroxypropylcellulose	50mg

talc	10mg
Total	500mg

compound 94	30mg
polyvinylpyrrolidone	25mg
lactose	385mg
hydroxypropylcellulose	50mg
talc	10mg
Total	500mg

(c) powder

compound 13	250mg
lactose	240mg
starch	480mg
colloidal silica	30mg
Total	1000mg

compound 65	300mg
lactose	230mg
starch	440mg
colloidal silica	30mg
Total	1000mg

compound 79	300mg
lactose	230mg

	starch	440mg
	colloidal silica	30mg
	Total	1000mg
	compound 100	300mg
	lactose	230mg
	starch	440mg
	colloidal silica	30mg
	Total	1000mg

(d) capsule

compound 13	50mg
lactose	102mg
crystalline cellulose	36mg
colloidal silica	2mg
Total	190mg
compound 23	100mg
lactose	52mg
crystalline cellulose	36mg
colloidal silica	2mg
Total	190mg
compound 74	200mg
glycerin	179.98mg

butyl p-hydroxybenzoate	0.02mg
Total	380mg

compound 81	30mg
glycerin	349.98mg
butyl p-hydroxybenzoate	0.02mg
Total	380mg

compound 98	200mg
glycerin	179.98mg
butyl p-hydroxybenzoate	0.02mg
Total	380mg

(2) Injection

(a) 1 to 30mg of compound 9B is contained in 1ml of the aqueous solution (pH 6.5-7.0).

(b) 1 to 30mg of compound 73 is contained in 1ml of the aqueous solution (pH 6.5-7.0).

(3) Ophthalmic solution

The following composition is contained in 5ml of the aqueous solution (pH 6.0).

Compound 23	50mg

	propyl p-hydroxybenzoate	0.7mg
	methyl p-hydroxybenzoate	1.3mg
	sodium hydroxide	proper quantity

(4) Ophthalmic ointment

The following composition is contained in 1g.

compound 22	20mg
white petrolatum	889.8mg
mineral oil	100mg
butyl p-hydroxybenzoate	0.2mg

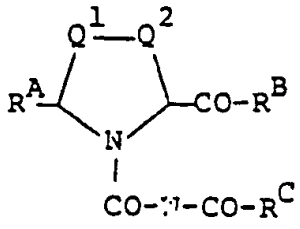
(5) Suppository

The following composition is contained in 1g.

compound 47	50mg
polyethylene glycol 1000	800mg
polyethylene glycol 4000	150mg

1 CLAIMS

1. A compound of the formula [I]



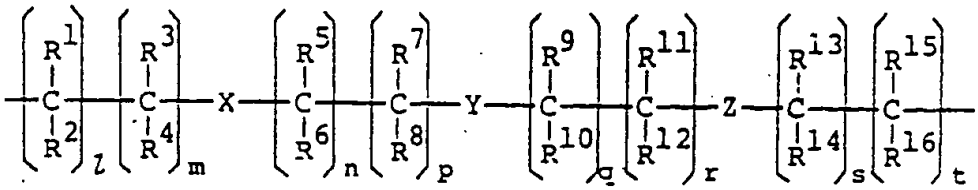
[I]

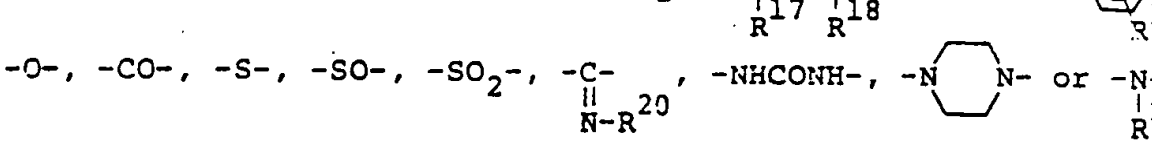
wherein

Q^1 and Q^2 each is methylene or sulfur, but Q^1 and Q^2 are not sulfur at the same time;

R^A is R^a or R^b;

R^B and R^C each is R^c;

W is  , wherein

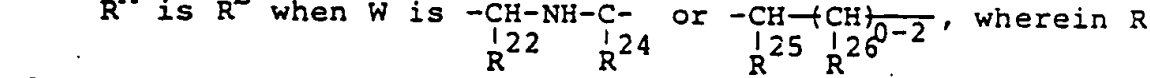
X,Y and Z each is single bond, $-CH_2-$, 

$-O-$, $-CO-$, $-S-$, $-SO-$, $-SO_2-$,

$-NHCONH-$, or ;

l, m, n, p, q, r, s and t each is 0, 1, 2 or 3;

R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20} and R^{21} each is R^d;

R^A is R^b when W is  or , wherein R^{22}, R^{23}, R^{24}, R^{25} and R^{26} each is R^d;

R^a is selected from the group consisting of

(i) hydrogen, lower alkyl and lower alkenyl, and

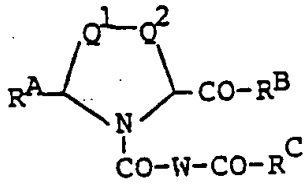
(ii) lower alkyl and lower alkenyl substituted by at least one substituent selected from the group consisting of lower alkyl,

1 TITLE OF INVENTION

THIAZOLIDINE AND PYRROLIDINE COMPOUNDS, PROCESSES FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

BACKGROUND OF INVENTION

This invention relates to thiazolidine and pyrrolidine compounds of the general formula



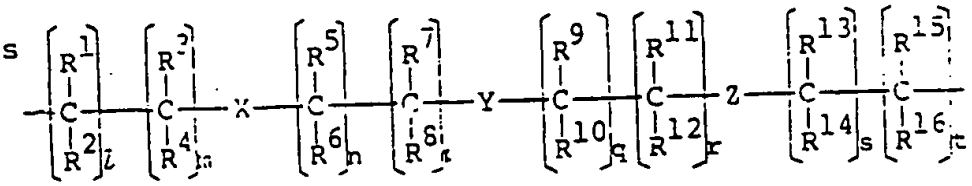
[I],

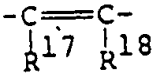
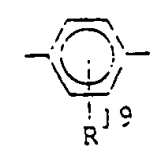
wherein

Q^1 and Q^2 each is methylene or sulfur, but Q^1 and Q^2 are not sulfur at the same time;

R^A is R^a or R^b;

R^B and R^C each is R^c;

W is  , wher

X, Y and Z each is single bond, $-CH_2-$,  , $-C\equiv C-$, 

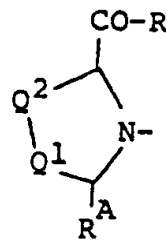
R^C is selected from the group consisting of

(a)(i) hydroxy, lower alkoxy and amino, and

(ii) lower alkoxy and amino substituted by at least one substituen selected from the group consisting of lower alkyl, aralkyl, heteroaralkyl, aralkenyl, heteroaralkenyl, hydroxy, lower alkoxy, aralkyloxy, heteroaralkyloxy, aryloxy, heteroaryloxy, acyloxy, aryl, heteroaryl, substituted aralkyl and substituted aryl wherein the substituent is lower alkyl, lower alkoxy, halogen or amino;

(b)(i) aryloxy and heteroaryloxy, and

(ii) aryloxy and heteroaryloxy substituted by at least one substituent selected from the group consisting of lower alkyl, hydroxy, lower alkoxy, halogen and amino, and

(c) 

;

R^d is selected from the group consisting of

(a)(i) hydrogen, lower alkyl, lower alkenyl, aralkyl, heteroaralkyl, alkanoyl, arylalkanoyl, heteroarylalkanoyl, hydroxy, carboxy, amino, mercapto and sulfo, and

(ii) lower alkyl, lower alkenyl, aralkyl, heteroaralkyl, alkanoyl, arylalkanoyl, heteroarylalkanoyl, hydroxy, carboxy, amino, mercapto and sulfo substituted by at least one substituent selected from the group consisting of lower alkyl, lower alkenyl, lower alkoxy, lower alkanoyl, aryl, heteroaryl, acyloxy, aroyl, hydroxy, carboxy, amino, guanidino, mercapto, acylamino, acylmercapto, lower alkoxycarbonyl, sulfo, halogen, nitro, cyano, sulfamoyl, lower alkylaminosulfonyl, lower alkylthio and lower alkylsulfinyl;

(b)(i) phenyl and naphthyl, and

(ii) phenyl and naphthyl substituted by at least one substituent

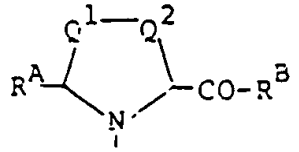
aryloxycarbonyl and heteroaryloxycarbonyl;

(b)(i) phenyl and naphthyl, and
(ii) phenyl and naphthyl substituted by at least one substituen selected from the group consisting of lower alkyl, lower alkenyl, halogeno-lower alkyl, hydroxy, lower alkoxy, halogeno-lower alkoxy, aralkyloxy, aryloxy, acyloxy, halogen, nitro, cyano, amino, lower alkylamino, dialkylamino, acylamino, mercapto, acylmercapto, lower alkylthio, carboxy, lower alkoxycarbonyl, aralkyloxycarbonyl, aryloxycarbonyl, sulfamoyl, lower alkylaminosulfonyl and lower alkylsulfinyl;

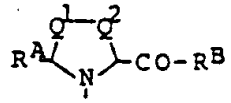
(c)(i) furyl, thienyl and pyridyl, and
(ii) furyl, thienyl and pyridyl substituted by at least one substituent selected from the group consisting of lower alkyl, lower alkenyl, halogeno-lower alkyl, hydroxy, lower alkoxy, halogeno-lower alkoxy, aralkyloxy, aryloxy, acyloxy, halogen, nitro, cyano, amino, lower alkylamino, dialkylamino, acylamino, mercapto, acylmercapto, lower alkylthio, carboxy, lower alkoxycarbonyl, aralkyloxycarbonyl, aryloxycarbonyl, sulfamoyl, lower alkylaminosulfonyl and lower alkylsulfinyl;

R^C is selected from the group consisting of
(a)(i) hydroxy, lower alkoxy and amino, and
(ii) lower alkoxy, and amino substituted by at least one substituent selected from the group consisting of lower alkyl, aralkyl, heteroaralkyl, aralkenyl, heteroaralkenyl, hydroxy, lower alkoxy, aralkyloxy, heteroaralkyloxy, aryloxy, heteroaryloxy, acyloxy, aryl, heteroaryl, substituted aralkyl and substituted aryl wherein the substituent is lower alkyl, lower alkoxy, halogen or amino;

(b)(i) aryloxy and heteroaryloxy, and
(ii) aryloxy and heteroaryloxy substituted by at least one substituent selected from the group consisting of lower alkyl, hydroxy, lower alkoxy, halogen and amino, and

(c)  ;

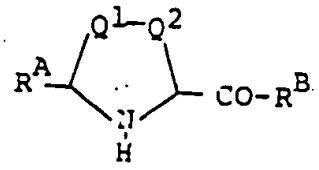
aminophenyl, 4-acetaminophenyl, 4-[(benzyloxycarbonyl)amino]phenyl, 2-carboxyphenyl, 4-carboxyphenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 3-benzoxyphenyl, 4-(benzyloxycarbonyloxy)-phenyl, 3,4-dihydroxyphenyl, 5-chloro-2-hydroxyphenyl, 2-methoxyphenyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, 3,4,5-trimethoxyphenyl, 2-hydroxy-3-methoxyphenyl, 2-hydroxy-4-methoxyphenyl, 4-hydroxy-3-methoxyphenyl, 3,4-methylenedioxyphenyl, 2-cyanophenyl, 3-cyanophenyl, 4-cyanophenyl, 2-nitrosophenyl, 3-nitrosophenyl, 4-nitrosophenyl, 2-hydroxy-5-sulfamoylphenyl, 2-hydroxy-5-[(dipropylamino)sulfonyl]phenyl, 3-(methylsulfinyl)phenyl, 3-(difluoromethoxy)phenyl, 1-naphthyl, 2-furyl, 2-(5-methyl)furyl, 2-thienyl, 3-pyridyl or 4-pyridyl.

5. A compound of claim 1 wherein R^C is hydroxy, methoxy, ethoxy, butoxy, amino, hydroxyamino, succinimidomethoxy, 1-succinimidoethoxy, phthalimidomethoxy, 2-phthalimidoethoxy, pivaloyloxymethoxy, 1-pivaloyloxyethoxy, benzyloxy, phenoxy, benzyloxyamino or  .

6. A compound of claim 1 wherein R^d is hydrogen, methyl, ethyl, propyl, 1-methylethyl, 2-methylpropyl, 4-methylpentyl, vinyl, allyl, 2-butenyl, 1,3-butanedienyl, 1-methylvinyl, hydroxymethyl, carboxymethyl, 2-carboxyethyl, cyclohexyl, cyclohexylmethyl, benzyl, 2-phenylethyl, 3-phenylbutyl, 2-(1-naphthyl)-ethyl, 2-(4-chlorophenyl)ethyl, 2-(3,4-dichlorophenyl)ethyl, 4-methoxybenzyl, 2-(4-methoxyphenyl)ethyl, 4-hydroxybenzyl, 2-(4-hydroxyphenyl)ethyl, (2-pyridyl)methyl, (4-pyridyl)-methyl, 2-(2-pyridyl)ethyl, 2-(4-pyridyl)ethyl, (4-imidazolyl)-methyl, 3-indolylmethyl, 2-(methylthio)ethyl, 4-aminobutyl, 5-aminopentyl, 4-guanidinobutyl, 4-(aminomethyl)benzyl, phenoxymethyl, (phenylthio)methyl, 1-amino-2-phenylethyl, 1-amino-3-methylbutyl phenyl, naphthyl, 4-methylphenyl, 2-chlorophenyl, 4-chlorophenyl, 2,4-dichlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-nitrophenyl, 3-nitrophenyl, 4-nitrophenyl, 2-chloro-5-nitrophenyl, 4-dimethylaminophenyl, 4-acetaminophenyl, 2-carboxyphenyl, 4-carboxyphenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 3-benzoxyphenyl, 3,4-

The compounds [I] of this invention can be prepared by following process.

(i) A compound of the formula [I] is yielded by the reactio of a compound of the formula [II]



[II],

wherein R^A and R^B may be protected by any suitable groups (e.g., lower alkyl, acyl, aralkyl, aralkyloxy, etc.) when R^A and R^B include reactive groups (e.g., amino, hydroxy, mercapto, hydroxyamino, etc.), with the reactive derivative of carboxylic acid of the formula [III] (e.g., acyl halide, acid anhydide, mixed anhydride, active ester, lactone, etc.) by general methods used in peptide syntheses or amide formation reactions

$$HOOC\text{-}W\text{-}CO\text{-}R^C \qquad [III],$$

wherein W and R^C may be protected by any suitable groups (e.g., lower alkyl, acyl, aralkyl, aralkyloxy, etc.) when W and R^C include reactive groups (e.g., amino, hydroxy, mercapto, hydroxyamino, etc.), followed by removal of protective groups by well-known methods (e.g., hydrolysis, hydrogenolysis, ammonolysis, alcoholysis, etc.).

This procedures of deprotection can be applied in the following methods.

10. A compound of claim 4 which is (4R,4'R)-3,3'-(nonanedioyl)bis[2-(3-nitrophenyl)-4-thiazolidinecarboxylic acid methyl ester].

11. A compound according to claim 4 which is (4R)-3-(11-carboxyundecanoyl)-2-(3-cyanophenyl)-4-thiazolidinecarboxylic acid;
(4R,4'R)-3,3'-(decanedioyl)bis[2-(3-cyanophenyl)-4-thiazolidinecarboxylic acid];
(4R,4'R)-3,3'-(dodecanedioyl)bis[2-(3-cyanophenyl)-4-thiazolidinecarboxylic acid;
(4R)-3-(8-carboxyoctanoyl)-2-(3-nitrophenyl)-4-thiazolidinecarboxylic acid;
(4R,4'R)-3,3'-(nonanedioyl)bis[2-(3-nitrophenyl)-4-thiazolidinecarboxylic acid];
(4R)-3-(7-carboxyheptanoyl)-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid.

12. A compound according to claim 4 which is (4R)-3-[[(1-carboxy-3-phenylpropyl)amino]acetyl]-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid;
(4R)-3-[[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]acetyl]-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid.

13. A compound according to claim 4 which is 1-[[(1-carboxy-3-phenylpropyl)amino]acetyl]-2-(2-hydroxyphenyl)-5-pyrrolidinecarboxylic acid;
1-[[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]acetyl]-2-(2-hydroxyphenyl)-5-pyrrolidinecarboxylic acid.

14. A compound of claim 4 which is (4R)-3-[[(1-carboxy-3-phenylpropyl)thio]acetyl]-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid.

15. A compound of claim 4 which is (4R)-3-(4-carboxybutanoyl)-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid.

protected such as (i) above, in the presence of proper alkaline and/or organic bases, if necessary, by known methods.

(iii) A compound of the formula [I] is yielded by the reaction of a compound of the formula [II] with the reactive derivative of carboxylic acid of the formula [VII] (e.g., metioned in (i) above)

$$HOOC-W^1-X-W^2-L \qquad [VII]$$

and then with a compound of the formula (VIII]

$$Y-W^3-Z-W^4-CO-R^C \qquad [VIII]$$

by the same method as (ii) above.

(iv) A compound of the formula [I] is yielded by the reaction of a compound of the formula [II] with the reactive derivative of carboxylic acid of the formula [IX] (e.g., mentioned in (i) above)

$$HOOC-W^1-X-W^2-Y-W^3-L \qquad [IX],$$

and then with a compound of the formula [X]

$$(H)Z-W^4-CO-R^C \qquad [X]$$

by the same method as (ii) above.

R^a is selected from the group consisting of
(i) hydrogen, lower alkyl and lower alkenyl, and
(ii) lower alkyl and lower alkenyl substituted by at least one substituent selected from the group consisting of lower alkyl, lower alkenyl, hydroxy, lower alkoxy, halogeno-lower alkoxy, acyloxy, halogen, nitro, cyano, amino, lower alkylamino, dialkylamino, acylamino, mercapto, acylmercapto, lower alkylthio, carboxy, lower alkoxycarbonyl, aralkyloxycarbonyl, aryloxycarbonyl, sulfamoyl, lower alkylaminosulfonyl and lower alkylsulfinyl;

R^b is selected from the group consisting of
(a)(i) aralkyl, heteroaralkyl, aralkenyl and heteroaralkenyl, and
(ii) aralkyl, heteroaralkyl, aralkenyl and heteroaralkenyl substituted by at least one substituent selected from the group consisting of lower alkyl, lower alkenyl, halogeno-lower alkyl, hydroxy, lower alkoxy, halogeno-lower alkoxy, acyloxy, halogen, nitro, cyano, amino, lower alkylamino, dialkylamino, acylamino, mercapto, acylmercapto, lower alkylthio, carboxy, lower alkoxycarbonyl, aralkyloxycarbonyl, aryloxycarbonyl, sulfamoyl, lower alkylaminosulfonyl and lower alkylsulfinyl, and
(iii) carboxy, lower alkoxycarbonyl, aralkyloxycarbonyl, aryloxycarbonyl and heteroaryloxycarbonyl;

(b)(i) phenyl and naphthyl, and
(ii) phenyl and naphthyl substituted by at least one substituent selected from the group consisting of lower alkyl, lower alkenyl, halogeno-lower alkyl, hydroxy, lower alkoxy, halogeno-lower alkoxy, aralkyloxy, aryloxy, acyloxy, halogen, nitro, cyano, amino, lower alkylamino, dialkylamino, acylamino, mercapto, acylmercapto, lower alkylthio, carboxy, lower alkoxycarbonyl, aralkyloxycarbonyl, aryloxycarbonyl, sulfamoyl, lower alkylaminosulfonyl and lower alkylsulfinyl;

(c)(i) furyl, thienyl and pyridyl, and
(ii) furyl, thienyl and pyridyl substituted by at least one substituent selected from the group consisting of lower alkyl,

reactive derivative of carboxylic acid of the formula [XV] (e.g., mentioned in (v) above)

$$HOOC\text{-}W^1\text{-}X\text{-}W^2\text{-}Y\text{-}W^3\text{-}Z(H) \quad [XV],$$

and then with a compound of the formula [XVI]

$$L\text{-}W^4\text{-}CO\text{-}R^C \quad [XVI]$$

by the same method as (ii) above.

(viii) A compound of the formula [I] is also yielded by converting a compound of the formula [I] prepared by any method above-mentioned by well-known methods (e.g., oxidation, formation of oxime, hydrazone and semicarbazone, addition to double bond, etc.)

The compounds [I] of this invention are effective on preventing or relieving diabetic complications.

In diabetic patients, high levels of hexoses (e.g., glucose, galactose, etc.) in blood lead to the accumulation of sugar alcohols (e.g., sorbitol, galactitol, etc.) in tissues. It is known that this accumulation causes the swelling of cells to induce complications of diabetic cataract, diabetic retinopathy, diabetic nephropathy, diabetic neuropathy, etc. [R. Quan-Ma et al., Biochem. Biophys. Res. Comm., 22, 492 (1966)]. For example, R. Gitzelman et al.

acylamino, acylmercapto, lower alkoxycarbonyl, sulfo, halogen, nitro, cyano, sulfamoyl, lower alkylaminosulfonyl, lower alkylthio and lower alkylsulfinyl;

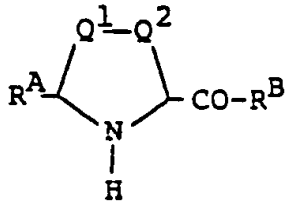
(b)(i) phenyl and naphthyl, and
(ii) phenyl and naphthyl substituted by at least one substituent selected from the group consisting of lower alkyl, lower alkoxy, lower alkanoyl, acyloxy, hydroxy, carboxy, amino, halogen, nitro, cyano, acylamino, mercapto, acylmercapto, halogeno-lower alkyl, halogeno-lower alkoxy, lower alkylenedioxy, lower alkoxycarbonyl, sulfo, sulfamoyl, lower alkylaminosulfonyl and lower alkylsulfinyl;

(c)(i) furyl, thienyl and pyridyl, and
(ii) furyl, thienyl and pyridyl substituted by at least one substituent selected from the group consisting of lower alkyl, lower alkoxy, lower alkanoyl, acyloxy, hydroxy, carboxy, amino, halogen, nitro, cyano, acylamino, mercapto, acylmercapto, halogeno-lower alkyl, halogeno-lower alkoxy, lower alkylenedioxy, lower alkoxycarbonyl, sulfo, sulfamoyl, lower alkylaminosulfonyl and lower alkylsulfinyl;

and salts thereof

which comprises

(i) reacting a compound of the formula [II]



[II]

wherein R^A and R^B may include suitable protection of any reactive groups with the reactive derivative of a carboxylic acid of the formula [III] (e.g., acyl halide, acid anhydride, mixed anhydride, active ester, etc.)

salts to be generally used as medicine such as sodium salt, potassium salt, calcium salt, magnesium salt, alminum salt, ammonium salt, diethylamine salt, triethanolamine, etc.

The compounds of formula [I] have the stereoisomers which are within the limit of this invention, because they have one or more asymmetric carbon atoms.

Typical examples are shown below, although this invention is not limited to these examples.

of any reactive groups, followed by removal of protective groups, if necessary, to yield a compound of the formula [I];

(iii) reacting a compound of the formula [II] with the reactive derivative of carboxylic acid of the formula [VII]

$$HOOC\text{-}W^1\text{-}X\text{-}W^2\text{-}L \qquad [VII],$$

and then with a compound of the formula [VIII]

$$(H)Y\text{-}W^3\text{-}Z\text{-}W^4\text{-}CO\text{-}R^C \qquad [VIII]$$

by the same method as (ii) above to yield a compound of the formula [I];

(iv) reacting a compound of the formula [II] with the reactive derivative of carboxylic acid of the formula [IX]

$$HOOC\text{-}W^1\text{-}X\text{-}W^2\text{-}Y\text{-}W^3\text{-}L \qquad [IX],$$

and then with a compound of the formula [X]

$$(H)Z\text{-}W^4\text{-}CO\text{-}R^C \qquad [X]$$

by the same method as (ii) above to yield a compound of the formula [I];

(v) reacting a compound of the formula [II] with the reactive derivative of carboxylic acid of the formula [XI]

$$HOOC\text{-}W^1\text{-}X(H) \qquad [XI],$$

and then with a compound of the formula [XII]

pyrrolidinc ring. The same shall be applied hereinafter

*2 Two spots were observed on the TLC (ethyl acetate-chloroform-acetic acid (10:5:3)), and two products could be separated by silica gel column chromatography From NMR spectra, the upper and lower spots were identified as the titled compound and (4R,4R')-3,3'-(octanedioyl)bis[2-(2-hydroxyphenyl)-4-thiazolidine-carboxylic acid] (compound 40), respectively.

*3 Silica gel, ethyl acetate-chloroform-acetic acid (10:5:3).

The compounds shown in Table I and III were prepared by the same procedure as described above.

The following compounds are also prepared by the same procedure as EXAMPLE 1.

(4R)-3-carboxyacetyl-4-thiazolidinecarboxylic acid

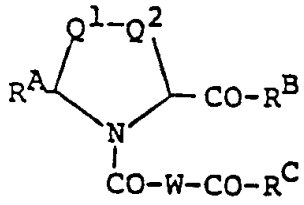
(4R)-3-(3-carboxypropanoyl)-2-phenyl-4-thiazolidine-carboxylic acid

(4R)-3-[3-(2-carboxyethylsulfinyl)propanoyl]-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid

(4R)-3-[[[2-(carboxymethyloxy)ethyl]oxy]acetyl]-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid

(4R)-3-(4-carboxybutanoyl)-2-(3-hydroxyphenyl)-4-thiazolidinecarboxylic acid

(4R)-3-(5-carboxypentanoyl)-2-(4-methylphenyl)-4-thiazolidinecarboxylic acid



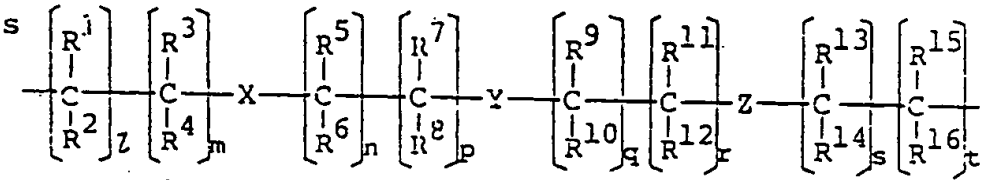
[I]

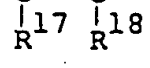
wherein

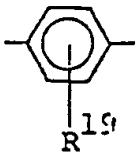
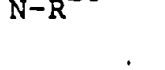
Q^1 and Q^2 each is methylene or sulfur, but Q^1 and Q^2 are not sulfur at the same time;

R^A is R^a or R^b;

R^B and R^C each is R^c;

W is  , where

X, Y and Z each is single bond, $-CH_2-$,  , $-C\equiv C-$,

 , $-O-$, $-CO-$, $-S-$, $-SO-$, $-SO_2-$,  , $-NHCONH-$,

thiazolidinecarboxylic acid

(4R)-3-(6-carboxyhexanoyl)-2-(2-furyl)-4-thiazolidine-carboxylic acid

(4R)-3-(7-carboxyheptanoyl)-2-(2-thienyl)-4-thiazolidine-carboxylic acid

(4R)-3-(8-carboxyoctanoyl)-2-(3-pyridyl)-4-thiazolidine-carboxylic acid

(4R)-3-(9-carboxynonanoyl)-2-(1-naphthyl)-4-thiazolidine-carboxylic acid

(4R)-3-(5-carboxypentanoyl)-2-(2-hydroxy-4-sulfamoyl-phenyl)-4-thiazolidinecarboxylic acid

(4R)-3-(6-carboxyhexanoyl)-2-(3-cyanophenyl)-4-thiazolidinecarboxylic acid

(4R)-3-(7-carboxyheptanoyl)-2-(3-difluoromethoxyphenyl)-4-thiazolidinecarboxylic acid

(4R)-3-(8-carboxyoctanoyl)-2-(4-carboxyphenyl)-4-thiazolidinecarboxylic acid

(4R)-3-(9-carboxynonanoyl)-2-(3-methylsulfinylphenyl)-4-thiazolidinecarboxylic acid

EXAMPLE 2

(4R,4'R)-3,3'-(Octanedioyl)bis[2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid (compound 40)

To a stirred solution of (4R)-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid (6.8g) in 1M potassium carbonate (45ml), octanedioyl dichloride (3.2g)

acylamino, mercapto, acylmercapto, lower alkylthio, carboxy, lower alkoxycarbonyl, aralkyloxycarbonyl, aryloxycarbonyl, sulfamoyl, lower alkylaminosulfonyl and lower alkylsulfinyl;

(c)(i) furyl, thienyl and pyridyl, and

(ii) furyl, thienyl and pyridyl substituted by at least one substituent selected from the group consisting of lower alkyl, lower alkenyl, halogeno-lower alkyl, hydroxy, lower alkoxy, halogeno-lower alkoxy, aralkyloxy, aryloxy, acyloxy, halogen, nitro, cyano, amino, lower alkylamino, dialkylamino, acylamino, mercapto, acylmercapto, lower alkylthio, carboxy, lower alkoxycarbonyl, aralkyloxycarbonyl, aryloxycarbonyl, sulfamoyl, lower alkylaminosulfonyl and lower alkylsulfinyl;

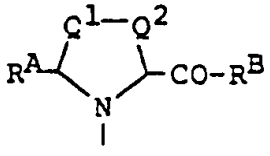
R^C is selected from the group consisting of

(a)(i) hydroxy, lower alkoxy and amino, and

(ii) lower alkoxy and amino substituted by at least one substituent selected from the group consisting of lower alkyl, aralkyl, heteroaralkyl, aralkenyl, heteroaralkenyl, hydroxy, lower alkoxy, aralkyloxy, heteroaralkyloxy, aryloxy, heteroaryloxy, acyloxy, aryl, heteroaryl, substituted aralkyl and substituted aryl wherein the substituent is lower alkyl, lower alkoxy, halogen, or amino;

(b)(i) aryloxy and heteroaryloxy, and

(ii) aryloxy and heteroaryloxy substituted by at least one subsituent selected from the group consisting of lower alkyl, hydroxy, lower alkoxy, halogen and amino, and

(c)  ;

R^d is selected from the group consisting of

(a)(i) hydrogen, lower alkyl, lower alkenyl, aralkyl, heteroaralkyl, alkanoyl, arylalkanoyl, heteroarylalkanoyl, hydroxy, carboxy, amino, mercapto and sulfo, and

organic layer was washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and evaporated in vacuo. The residual oil was purified by silica gel column chromatography to give 7.6g (86%) of the titled compound: mp 93-97°C (dec.); $[\alpha]_D^{27}$ +123.6° (c=0.5, methanol). IR (nujol, cm^{-1}): 1720 (COOH), 1620 (CON), 1600 (aromatic), 1230, 1090, 855, 765. MNR (CD_3OD) δ: 0.7-1.7 (8H, m, $-CH_2\underline{(CH_2)_4}CH_2-$), 1.8-2.4 (4H, m, $-\underline{CH_2}(CH_2)_4\underline{CH_2}$), 3.25 (4H, d, J=7.5Hz , C_5-H), 4.81 (2H, t, J=7.5Hz, C_4-H), 6.35 (2H, s, C_2-H), 6.7-8.0 (8H, m, arom. H). TLC: Rf value* 0.34.

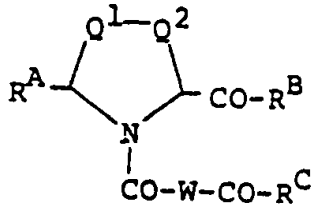
* Silica gel, ethyl acetate-chloroform-acetic acid (10:5:3).

The compounds shown in Table II and III were prepared by the same procedure as described above.

EXAMPLE 3

(4R,4'R)-3,3'-(heptanedioyl)bis[2-(3-cyanophenyl)-4-thiazolidinecarboxylic acid] (compound 36)

To a stirred solution of (4R)-2-(3-cyanophenyl)-4-thiazolidinecarboxylic acid (4.7g) in 1M sodium carbonate (30ml), heptanedioyl dichloride (2.1g) was added dropwise under ice-cooling. The reaction mixtur was stirred for 30 minutes at the same temperature, and



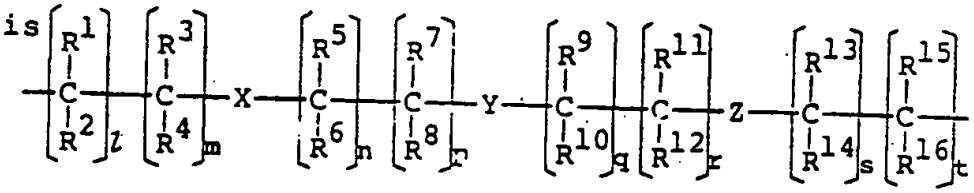
[I]

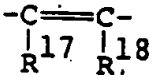
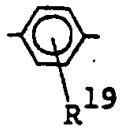
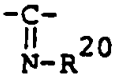
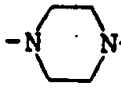
wherein

Q^1 and Q^2 each is methylene or sulfur, but Q^1 and Q^2 are not sulfur at the same time;

R^A is R^a or R^b;

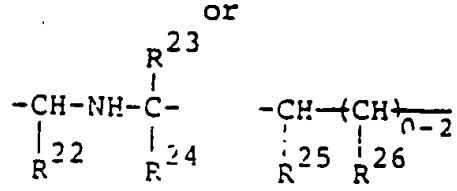
R^B and R^C each is R^c;

W is  , wherein

X, Y and Z each is single bond, $-CH_2-$,  , $-C\equiv C-$,  , $-O-$, $-CO-$, $-S-$, $-SO-$, $-SO_2-$,  , $-NHCONH-$,  or  ;

ℓ, m, n, p, q, r, s and t each is 0, 1, 2 or 3;

R^1, R^2, R^3, ..., R^{20} and R^{21} each is R^d;

R^A is R^b when W is  or , wherein R^{22},

(4R,4'R)-3,3'-(pentanedioyl)bis[2-(3-hydroxyphenyl)-4-thiazolidinecarboxylic acid]

(4R,4'R)-3,3'-(hexanedioyl)bis[2-(4-methylphenyl)-4-thiazolidinecarboxylic acid]

(4R,4'R)-3,3'-(heptanedioyl)bis[2-(4-chlorophenyl)-4-thiazolidinecarboxylic acid]

(4R,4'R)-3,3'-(octanedioyl)bis[2-(4-methoxyphenyl)-4-thiazolidinecarboxylic acid]

(4R,4'R)-3,3'-(tetradecanedioyl)bis[2-(2-nitrophenyl)-4-thiazolidinecarboxylic acid]

(4R,4'R)-3,3'-(3,3'-thiodipropanoyl)bis[2-(3-nitrophenyl)-4-thiazolidinecarboxylic acid]

(4R,4'R)-3,3'-[(ethylenedioxy)diacetyl]bis[2-(3-nitrophenyl)4-thiazolidinecarboxylic acid]

(4R,4'R)-3,3'-(heptanedioyl)bis[2-(4-nitrophenyl)-4-thiazolidinecarboxylic acid]

(4R,4'R)-3,3'-(decanedioyl)bis[2-(4-nitrophenyl)-4-thiazolidinecarboxylic acid]

(4R,4'R)-3,3'-(dodecanedioyl)bis[2-(4-nitrophenyl)-4-thiazolidinecarboxylic acid]

(4R,4'R)-3,3'-(4,4'-oxydibutanoyl)bis[2-(4-nitrophenyl)-4-thiazolidinecarboxylic acid]

(4R,4'R)-3,3'-(3,3'-sulfonyldipropanoyl)bis[2-(4-nitrophenyl)-4-thiazolidinecarboxylic acid]

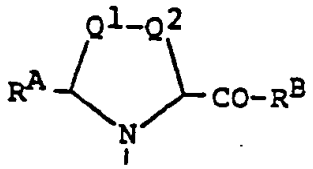
(4R,4'R)-3,3'-(decanedioyl)bis[2-(5-chloro-2-hydroxyphenyl)-4-thiazolidinecarboxylic acid]

(4R,4'R)-3,3'-(dodecanedioyl)bis[2-(3,4,5-trimethoxyphenyl)-4-thiazolidinecarboxylic acid]

(c)(i) furyl, thienyl and pyridyl, and
(ii) furyl, thienyl and pyridyl substituted by at least one substituent selected from the group consisting of lower alkyl, lower alkenyl, halogeno-lower alkyl, hydroxy, lower alkoxy, halogeno-lower alkoxy, aralkyloxy, aryloxy, acyloxy, halogen, nitro, cyano, amino, lower alkylamio, dialkylamino, acylamino, mercapto, acylmercapto, lower alkylthio, carboxy, lower alkoxycarbonyl, aralkyloxycarbonyl, aryloxycarbonyl, sulfamoyl, lower alkylsulfonyl, and lower alkylsulfinyl;

R^C is selected from the group consisting of
(a)(i) hydroxy, lower alkoxy and amino, and
(ii) lower alkoxy and amino substituted by at least one substituent selected from the group consisting of lower alkyl, aralkyl, heteroaralkyl, aralkenyl, heteroaralkenyl, hydroxy, lower alkoxy, aralkyloxy, heteroaralkyloxy, aryloxy, heteroaryloxy, acyloxy, aryl, heteroaryl, substituted aralkyl and substituted aryl wherein the substitutent is lower alkyl, lower alkoxy, halogen or amino;

(b)(i) aryloxy and heteroaryloxy, and
(ii) aryloxy and heteroaryloxy substituted by at least one substituent selected from the group consisting of lower alkyl, hydroxy, lower alkoxy, halogen and amino, and

(c) 

;

R^d is selected from the group consisting of
(a)(i) hydrogen, lower alkyl, lower alkenyl, aralkyl, heteroaralkyl, alkanoyl, arylalkanoyl, heteroarylalkanoyl, hydroxy, carboxy, amino, mercapto and sulfo, and
(ii) lower alkyl, lower alkenyl, aralkyl, heteroaralkyl, alkanoyl, arylalkanoyl, heteroarylalkanoyl, hydroxy, carboxy, amino, mercapto and sulfo substituted by at least

reaction mixture was stirred for 1 hour at the same temperature, and the separated crystals were filtered to give 4.7g (69%) of the titled compound as disodium salt: mp 111-113°C (dec.) (water); $[\alpha]_D^{25}$ +88.2° (c=0.5, methanol) IR (nujol, cm^{-1}): 1635 (CON), 1585 (COO^-), 1520 and 1355 (NO_2), 1095, 730. TLC: Rf value* 0.28.

* Silica gel, ethyl acetate-chloroform-acetic acid (10:5:3).

EXAMPLE 5

(4R)-3-(3-Carboxypropanoyl)-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid (compound 6)

To a stirred solution of (4R)-2-(2-hydroxyphenyl)-4-thiazolidinecarbcxylic acid (4.5g) and triethylamine (4.0g) in acetone (100ml), succinic anhydride (2.0g) was added at room temperature, and stirred for 3 hours at the same temperature. The reaction mixture was concentrated in vacuo, and acidified with dilute hydrochloric acid. The separated oil was extracted with ethyl acetate, and the organic layer was washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and evaporated in vacuo to give 4.9g (75%) of the titled compound: mp 190-191°C (dec.) (ethyl acetate-methanol); $[\alpha]_D^{27}$ +181.6° (c=1.0, methanol). IR (nujol, cm^{-1}): 3210

After the addition, the reaction mixture was stirred for 1.5 hours at the same temperature. After the filtration of solution, the filtrate was acidified with dilute hydrochloric acid, and extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and evaporated in vacuo. The residual oil was purified by silica gel column chromatography to give 7.8g (44%) of the titled compound: $[\alpha]_D^{25}$ +161.6° (c=1.0, methanol). IR (KBr, cm^{-1}): 3380 (OH), 1723 (COOH, $COOCH_3$), 1624 (CON), 1235, 1200, 1174, 764.

The compounds shown in Table I and II were prepared by the same procedure as described above.

EXAMPLE 7

(4R)-3-(3-Carboxy-2-methylpropanoyl)-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid (compound 5)

(4R)-3-[3-(Methoxycarbonyl)-2-methylpropanoyl]-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid (compound 4) (7.1g) was dissolved in 2N sodium hydroxide (40ml) and stirred for 1 hour at room temperature. The resulting solution was acidified with dilute hydrochloric acid and the separated crystals were filtered to give 5.1g (75%) of the titled compound: mp 163-164°C (dec.)

European Patent Office

EUROPEAN SEARCH REPORT

Application number

EP 80 10 7869

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl. ³)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
P	FR - A - 2 445 324 (SANTEN PHARM) *"Revendications"* --	1-5	
P	FR - A - 2 440 365 (SANTEN PHARM) *"Revendications"* --	1-5	
P	FR - A - 2 434 150 (YOSHITOMI PHARM.) *"Revendications"* ----	1-5	TECHNICAL FIELDS SEARCHED (Int. Cl. ³)

European Patent Office

EUROPEAN SEARCH REPORT

Application number
EP 80 10 7869

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim
*	US - A - 4 154 937 (D.W. CUSHMAN et al.) * Columns 1-2 *	1-3,5, 6,7, 16
*	GB - A - 2 000 508 (YOSHITOMI PHARM. LTD.) * Pages 1-2 *	1-5, 7,16
	FR - A - 2 407 204 (SANDOZ S.A.) *"Revendications"*	1-5
	FR - A - 2 412 537 (SCIENCE UNION ET CIE) *"Revendications"*	1,2
	FR - A - 2 340 933 (E.R.SQUIBB AND SONS) *"Revendications"*	1-3, 5-7
	FR - A - 2 340 932 (E.R SQUIBB AND SONS) *"Revendications"*	1-3, 5-7
	FR - A - 2 023 741 (EPROVA AG) *"Revendications"*	1
P	EP - A - 0 007 477 (DAINIPPON PHARM) *"Revendications"* ./.	1-5

CLASSIFICATION OF THE APPLICATION (Int. Cl.³)

C 07 D 277/06
207/16
A 61 K 31/425
31/40

TECHNICAL FIELDS SEARCHED (Int. Cl.³)

C 07 D 277/06
277/16

CATEGORY OF CITED DOCUMENTS

X: particularly relevant
A: technological background
O: non-written disclosure
P: intermediate document
T: theory or principle underlying the invention
E: conflicting application
D: document cited in the application
L: citation for other reasons

&: member of the same patent family, corresponding document

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
The Hague	09-03-1981	BRIGHENTI